

THE ASSOCIATION OF OLIGOPHRENIA AND DYSKERATOSES
A Clinical Investigation and an Enquiry into its Implications

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by

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FOREWORD

The origin of the present study lies in the admission in 1949 of a certain patient to a psychiatric hospital where he was placed in my care. He suffered from a combination of mental deficiency, epilepsy, ichthyosis and hypogenitalism. I recognised that this constituted a syndrome described in Tredgold's Textbook (1947), and on searching the literature I discovered that only five reports of such cases had been published. In this reading I noted that numerous references have been made to an association between certain skin diseases and oligophrenia, but that few systematic surveys have been carried out. This led to the work which is now reported for the first time. Here, I am reviewing the literature, reporting the results of some controlled clinical investigations and discussing the implications of these findings.

INTRODUCTION

Tredgold, the authority on mental deficiency, notes in his text book (1947) that certain skin anomalies are found in association with oligophrenia. He mentions coarseness, excessive and unpleasant secretion, webbing of fingers, moles, naevi, excessive hair on parts usually hairless, lack of hair, malformed nails and adenoma sebaceum.

No adequate classification of these skin conditions has yet been achieved, nor is their aetiology clear at present. Nevertheless, as will be shown in this paper, various authors have recognised the importance of skin diseases in association with mental deficiency. Recently, in suggesting a tentative clinical classification of the specific types of mental deficiency, Gibson (1950) has recognised the need for including a "cutaneous group" among his six basic groups.

At the present time we lack any single source which summarises the vast literature on the subject, and the present paper is an attempt to supply this in part. In addition I found that no-one has compared the skins of mental defectives with a control group of non-mental defectives, and therefore I undertook this work.

After preliminary survey I confined my work to the various conditions which may be broadly classified as dyskeratoses. Other conditions such as tuberous sclerosis with adenoma sebaceum, naevoid amentia and neurofibromatosis are sufficiently recognised clinical entities. (Yakovlev and Guthrie, 1931; Bogaert, 1935.)

The first part of the paper is therefore concerned with certain dyskeratoses, their clinical description, discussion of aetiology and genetics, and their reported associations with mental deficiency.

ICHTHYOSIS

This abnormal skin condition has been described on many occasions with various subdivisions. Milder forms of the same disease are called xeroderma by some authors (Walker, 1925; Semon and Moritz, 1946).

The ichthyotic skin is dry, scaly and tends to look dirty. There may be associated keratosis follicularis. In ichthyosis vulgaris or simplex the skin of the flexures, axillae, groins, in front of the elbows and behind the knees is often smooth and supple. The sites of maximal dryness and fish-like scaliness are usually over the knees and elbows and extensor surfaces. (Cockayne, 1933). The condition is usually fully developed by the age of 10 years.

In ichthyosis there is frequently a diminished or absent ability to sweat. It may be relevant to note that this feature is prominently seen in another condition which is associated with oligophrenia and will be discussed later - anhidrotic ectodermal dysplasia. Histologically, Percival, Drennan and Dodds (1947) noted that in ichthyosis the sebaceous and sweat glands are scanty.

Sequiera (1927) defines ichthyosis as a hyperkeratosis of the horny layers of the skin which is often congenital, and is endemic in some tribes. He mentions the use of thyroid extract in treatment, as do other authors, none of whom claims any great improvement. Cranston Low (1934) recommended the use of thyroid early in the disease if results are to be at all good. He pointed out that typical ichthyosis appears some weeks or months after birth, and postulated that previously the skin had been kept normal by stored maternal thyroxine. In connection with this it is relevant to note the case of Helman (1947)

who described sporadic cretinism and ichthyosis in the same family. The first child of normal parents was cretinous, the second and third were normal and the fourth had ichthyosis.

Porter (1926) studied cases of ichthyosis (and the patients' mothers in some instances) with special reference to the basal metabolic rate. He noted a lowered B. M. R. in 7 out of 10 children, and was of the opinion that in such patients the ichthyosis responded better to thyroid than it did in patients with a normal or raised B. M. R. Following the line of thought of Thomson and Wakeley (1921) (who postulated a maternal hyperthyroidism which might lead to foetal hypothyroidism) Porter measured the B. M. R. in six mothers of ichthyotic children and found it raised in four cases. In his article Porter quotes several instances in which ichthyosis has been described alongside myxoedema.

The absence of true ichthyosis in known cases of hypothyroidism and the lack of response to thyroid have been attributed by Porter to the fact that some other factor than thyroxine is involved. He refers to the work of Kendall (1915) in which two groups of thyroid proteins were isolated, only one of which was said to be effective in "certain skin conditions" (unspecified). No later work appears to have been done on this subject, although it is now recognised that two types of thyroxine (d- and l-) occur, and that the l- form is more active. (Griesbach et al., 1949).

Rapaport et al. (1942) treated six individuals suffering from ichthyosis with prolonged large doses of vitamin A, and obtained improvement. Five of these patients also showed dark dysadaptation,

which also improved. These writers concluded that in ichthyosis there may be a hereditary disorder of vitamin A metabolism.

Semon and Moritz (1946) suggested the possibility of a vitamin A deficiency and the use of the vitamin in all cases of acquired ichthyosis. This was also referred to by Glazebrook and Tomazewski (1947) and Peck, Glick and Chargin (1943). The latter studied the question of vitamin A deficiency in congenital ichthyosis and found the eruption little influenced by large doses of the vitamin. However, they concluded that a disturbance of vitamin A metabolism was present but that its relation to the ichthyotic changes was not clear.

Coste, Piguet and Civatte (1952) report a case of ichthyosis vulgaris improved with cortisone, and showing reappearance of cutaneous secretory functions.

Nelson (1953) believes that the skin condition of pachyderma is probably due to dietary deficiency of unsaturated fatty acids. A climatic factor is also involved, but the thickened, roughened skin appears to improve when ground nut oil or fish is included in the diet.

In discussing the disease Glazebrook and Tomazewski (1947) pointed out that ichthyosis may develop as a result of toxic processes, particularly such as may affect the nervous system. For example they instanced the association of localised ichthyosis and neuritis from a preceding disease or injury, but they concluded that there was no evidence to implicate the nervous system as a causal factor in the generalised type of ichthyosis. Finally, mention must be made of the remarkable alleviation produced by Mason (1952) in a case of generalised congenital ichthyosis treated by suggestion under hypnosis. Undoubtedly this

report must lead to further studies into the causal factors of ichthyosis. In the meantime it seems possible that the nervous system is indeed involved in generalised ichthyosis.

At the present moment, however, the condition of ichthyosis cannot be attributed to any one cause. It undoubtedly occurs as a hereditary defect in some cases. Whether it is an abnormality of skin development, or is secondary to some other derangement, such as a metabolic disorder, remains obscure.

GENETICS OF ICHTHYOSIS

Ichthyosis vulgaris. The genetics of ichthyosis is somewhat confused owing to the fact that different forms have been described and nomenclature varies from country to country. In the case of ichthyosis vulgaris the condition is said to occur in a sex-linked recessive form mainly in Latin countries (Levit, 1936; Harris, 1947) and to be mainly dominant in Northern Europe (Cockayne, 1933). Davies and McGregor (1942) described an undoubted example of hologynic inheritance of this disease through three generations. The condition not infrequently skips a generation and Gates (1946) postulated that there may be an inhibiting gene responsible for this.

Ichthyosis congenita. Cockayne describes ichthyosis congenita as beginning with a redness of the skin and progressing to a state of thickening and scaliness. The skin is affected symmetrically almost throughout the body, whereas ichthyosis vulgaris usually spares the flexures of the limbs. This condition appears as an autosomal recessive due to a single gene and shows a small excess of males over females.

ASSOCIATION OF ICHTHYOSIS AND OLIGOPHRENIA

Ichthyosis vulgaris. Most of the classic descriptions of ichthyosis by dermatologists make no reference to the mental state of the patient. Where this is mentioned it is often poorly described. From the literature, therefore, it is impossible to estimate the frequency of oligophrenia in ichthyosis. In any case, doubtless only severe mental defect would have been noted by most of the authors. Nevertheless one can find several instances in which authors have been impressed by such an association.

A pedigree traced by Boeck and cited by Orel (1929) shows associated ichthyosis and mental deficiency going back to 1680.

Henrichs (1920) has studied seven Norwegian families in which the two conditions appeared - 21 subjects were imbeciles, 17 had ichthyosis, and both conditions were present in 10 cases. He believed that both the skin and mental changes were due to an ectodermal defect carried by a single gene. In reviewing this paper Cockayne (1933) suggested two other possibilities, namely chance, or the presence of two independent genes in the same chromosome.

In 1908 Vincent presented two cases to show that there might be some association between ichthyosis and thyroid dystrophy, and noted that one of his two cases was of "rudimentary intelligence".

Porter (1926) cited similar cases described by Weill and Cramer.

Developmental abnormalities associated with ichthyosis vulgaris have been reviewed by Sundt (1947). Out of 18 of his own cases 5 showed abnormalities - 1 had pseudohermaphroditism, 1 albinism, 2 brothers had deformed ears and one aged 28 had arcus senilis as well. The fifth patient had reduced mental powers, skeletal changes and small stature, and there was a family history of ichthyosis and imbecility.

In a review of the nervous system in ichthyosis, Laubenthal (1940) referred to the occurrence of feeble-mindedness with ichthyosis, but pointed out that some inherited symptoms not of ectodermal origin are associated with ichthyosis. These include polydactyly, arachnodactyly, endocrine disorders such as diabetes, endogenous adiposity and derangements of the genital apparatus. He postulated that the disorders may have a common functional basis with the point of attack in the diencephalic-hypophyseal system. Cockayne (1933) noted similar associations between ichthyosis and polydactyly, acromegaly, Grave's disease and infantilism.

The association of mental deficiency, epilepsy, ichthyosis and infantilism was first recorded by Einar Rud in 1927. The syndrome of Rud has reached some of the text books on mental deficiency, and five examples of the syndrome have been described in the literature. I have discovered five new cases of this syndrome, four of them in the survey of mental defectives' skins reported in this paper. These cases will be described later and the Syndrome of Rud discussed more fully then.

Engler (1949) in his book on mongolism goes into detail concerning the skin changes. He finds that the skin, although normal at birth, shows marked changes after a few years. The skin turns dull, loses its softness and elasticity, and becomes dry and hard. Secretion of sebum and sweat decreases considerably, in some cases ceasing altogether. The hard coarse skin presents considerable thickening, particularly on the back of the hands and over the heels and knees. Though scale-formation and desquamation have been denied by several authors, Engler has observed many older mongol idiots with marked scale-formation.

He finds also a tendency to all kinds of irritations and eczemas, ranging from simple dermatitis to severe ichthyosis. The nails are usually brittle, pale and often appreciably thickened. Hair usually becomes hard, dry and sparse.

Ichthyosis congenita. (Ichthyosiform erythroderma)

Cockayne (1933) states that many patients with this condition are of good physique and average intelligence. Of the 253 cases he reviews, 6 are specifically noted as having shown physical and mental underdevelopment. Touraine (1947) states that such an association is often found.

A case described by Fitzgerald and Booker (1951) is of interest because of the cerebral changes found at post-mortem examination. This was a male infant, the second child of a 17 year old mother. At birth there was intense redness of the cheeks, anterior aspects of the chest and knees and lateral surfaces of the arms. By the seventh day the skin was dry and scaly and more extensively involved. Skin changes persisted in spite of ointments, large doses of vitamin A and multivitamins. The infant's nutrition was always poor and he failed to gain weight adequately, in spite of being under full hospital care for months. The erythema decreased in severity with age, whereas the keratotic changes increased. At the age of 15 months the child suffered from an attack of Kaposi's varicelliform eruption, and seven months later he died.

Autopsy revealed underdevelopment of all portions of the body and generalised lymphadenopathy. There was microgyria of the 2 left superior temporal convolutions, also of the left second and third frontal

convolutions. The anterior portion of the left corpus striatum was absent, including the internal capsule, except for a small inferior tip of the caudate nucleus. Compensatory dilatation of the left lateral ventricle was present, and there was thickening, oedema and leukocytic infiltration of the meninges, particularly in the region of the microgyria. Just below the meninges in the area of the microgyria there was degeneration, softening and vacuolisation of the parenchyma without demonstrable vascular changes.

The first child of the same parents had been previously diagnosed as a case of ichthyosis, but after the birth of the child who died it was realised that both suffered from ichthyosiform erythroderma as described by Brocq (1902). The first child was otherwise normal mentally and physically, and a third child was born without sign of the skin disease.

Consanguinity and a tendency to inheritance as a recessive trait have been noted. In this instance the parents were third cousins.

The above findings suggest, without offering statistical proof, that the association of oligophrenia with ichthyosis vulgaris and congenita may be commoner than would be expected by chance.

The ichthyoses are usually classified as dyskeratoses or hyper-ectodermoses, other examples of which will now be considered.

DARIER'S DISEASE
(keratosis follicularis)

In this condition there is a cellular degeneration at the upper third of some of the pilo-sebaceous follicles and openings of sweat ducts. Papules appear at these points and, later, papillated excrescences develop on the moister parts. These changes can occur on the scalp, face, back, abdomen, flexures of the limbs, inguinal areas and genitals. Some examples show a linear distribution and, more rarely, a nerve or segmental distribution (Cockayne).

Microscopic examination shows an abnormal keratinisation of individual rete cells, and horny plugs (corps ronds) of dyskeratotic cells in the deeper parts of the epidermis (Percival et al, 1947).

Working on vitamin A deficiency in rats, Sullivan and Evans (1945) concluded that excessive hyperkeratinisation is associated with the deficiency, and is made worse by concomitant vitamin B group deficiency. They were wary about applying these results to humans by analogy.

Frazier, Hu and Chu (1943) in their studies of the cutaneous manifestations of vitamin A deficiency in childhood, noted that the earliest sign was a simple xerosis of the surface epithelium. This led to a progressive development of follicular hyperkeratosis with increasing age, particularly towards puberty. They did not include cases of keratosis pilaris (described below), and concluded that the full follicular eruption characteristic of vitamin A deficiency only occurs with attainment of sexual maturity. This is an interesting finding as it corresponds with the clinical results to be reported later in this paper. Peck, Glick, Sobotka and Chargin (1943) treated cases of Darier's disease with 200,000 U. S. P. Units of vitamin A daily. Nine out of ten cases

improved, but showed a gradual recurrence when the additional vitamin was withdrawn, in spite of continued adequate diet. These workers postulated a hereditary or acquired weakness in absorption of provitamin A which reflects itself in the skin as a dyskeratosis.

Because of this and other papers reporting improvement with vitamin A, Leitner and Moore (1948) postulated a functional impairment of the liver. They found some evidence of this, using the hippuric acid test, in 5 out of 6 cases of Darier's disease. However, a further investigation by Porter and Brunauer (1949), using a battery of liver tests, failed to reveal evidence of hepatic dysfunction in 6 cases, and 4 out of 5 cases showed a normal level of vitamin A in the plasma.

Working among malnourished tribes in Nigeria, Nicol (1949) concluded that vitamin A deficiency results in dryness and depigmentation of the hair, generalised xerosis, elephant skin, crackled skin, night blindness and follicular hyperkeratosis. He defines the latter as marked thickening of follicles and projecting spiny plugs of keratinised material superimposed upon a general xerosis. This is to be distinguished from the simple enlargement or undue prominence of the follicles seen in keratosis pilaris, which, Nicol believes, is not associated with vitamin A deficiency. The contention of Stannus (1945) is, however, that so-called cases of keratosis follicularis are really only examples of the common keratosis pilaris.

On the other hand the American Medical Association Council on Foods and Nutrition (1946) concluded that the papular eruption of keratosis pilaris, and also simple xerosis, were attributable to vitamin A deficiency.

In another study of Nigerian peasants, Nicol (1952) confirmed his earlier conclusions. He did, however, also find examples of xerosis, elephant skin and crackled skin in tribes with an ample intake of carotene. This led him to conclude that these changes may result from vitamin C deficiency, or an inability to utilise vitamin A as a result of liver disturbances or lack of fat to aid absorption of carotene.

When Crandon, Lund and Dill (1940) studied experimental human scurvy induced in Crandon himself, it was noticed that, after 134 days, small perifollicular hyperkeratotic papules associated with dry skin began to develop over the buttocks and posterior aspects of the calves. These lesions progressed and resembled a mild form of the lesions described as typical of vitamin A deficiency. At the conclusion of the experiment the hyperkeratosis cleared quickly when the subject received ascorbic acid.

In the Medical Research Council's (1949) report on vitamin A deficiency it is stated that enlargement and hyperkeratosis of hair follicles occurred among subjects of both control and experimental groups. The lesions seemed to fluctuate independently of the state of vitamin A nutrition. It was concluded that there was lack of evidence that vitamin A deficiency is the specific causal factor in development of follicular hyperkeratosis.

In a more recent paper, Leitner (1951) continues to report considerable improvement of Darier's disease treated with vitamin A. He refers again to the association of disturbed vitamin A metabolism with hepatic diseases. He attributes the failure of Porter and Brunauer (1949) to confirm his previous work to the fact that they used different liver function tests. Leitner draws an analogy between the induction of congenital anomalies by maternal rubella,

and deficiency of specific nutrients during pregnancy producing the same effect.

This latter possibility has been demonstrated in rats by Wilson and Warkany (1949 and 1950). They found anomalies of development of the 4th. branchial arteries in rats born of vitamin A deficient mothers. This is referred to by Mautner (1951) in an interesting study of mongolism. Mautner shows that heart malformations occur in from 30 to 70 per cent of mongoloids, and that the condition of ostium atrioventriculare commune (which has been found only in mongoloids up to the present) is similar to the defects in rats born of vitamin A deficient mothers.

In concluding his paper referred to above, Leitner suggests that all pregnant women with infection or fever, particularly in the first trimester, should receive 40-50,000 i.u. of vitamin A daily. He bases this on the fact that plasma levels of vitamin A diminish under these conditions. This is an interesting proposal, but obviously only a large-scale controlled experiment such as might be conducted by the Medical Research Council could show the presence or lack of effect.

Goodman (1938) reported improvement in keratinised pilosebaceous apertures of the upper arms and thighs of young girls who were placed on improved diets with vitamin A content. He got similar excellent results with 1 gr. of whole pituitary gland daily, by mouth. Goodman goes on to ask the question: "Will a relationship be established between the pituitary hormones and vitamin A?"

Working experimentally with rats in the study of phrynoderma (toad skin) which is similar to keratosis follicularis, Ramalingaswami and Sinclair (1953) conclude that deficiency of essential

fatty acids may be the cause of the condition in man.

Bearing in mind the fluctuations noticed during the Medical Research Council's careful study, it is apparent that we must accept therapeutic claims with great caution in Darier's disease.

Darier's disease of the skin must therefore be considered to be of unknown origin at present, although there may be a nutritional factor involved.

Genetically Darier's disease is transmitted as a dominant character (Gates, 1946), although irregularly dominant in some cases, and it has been known to arise de novo by mutation. Owing to lack of reproduction by sufferers, the condition tends to die out.

ASSOCIATION OF DARIER'S DISEASE WITH OLIGOPHRENIA

Cockayne (1933) states that in Darier's disease small stature and mental deficiency have been noticed in such large numbers that they must be regarded as part of the fully developed and severest form of the disease.

Cockayne discusses separately a condition which is called alternatively keratosis follicularis or pachyonychia congenita. The skin changes are similar to those in Darier's disease and some authors regard both conditions as the same, while others do not find corps ronds in pachyonychia congenita. Pachyonychia is described as being present at

birth in nearly every case, and some cases also show hyperkeratosis of the skin of the palms and soles. Among 27 recorded cases reviewed by Cockayne is a boy described by Brunauer (1924) who was mentally defective.

Allan, Herndon and Dudley (1944) include Darier's disease and anhidrotic ectodermal dysplasia (which will be described shortly) in their list of genetic conditions primarily affecting other functions but also involving mental functions.

TYLOSIS PALMARIS ET PLANTARIS

This condition is also known as ichthyosis or keratosis palmarum et plantarum.

The great thickening of the palmar and plantar skin may be present at birth, or may develop around 3 to 12 months of age, and has been noted as having an onset at 15 years. Most cases suffer from hyperhidrosis and the nails may be curved and overgrown. The general health is usually unaffected, but Cockayne (1933) cites 2 cases of Mierzecki who were mentally backward and had hypogenitalism, one case of Giese showing oxycephaly and one of Sutejev suffering from infantilism and mental inertia.

Although solitary cases have been recorded, the abnormality is usually transmitted directly from parent to offspring.

Thatcher (1912) reported three children from Shetland who showed the skin condition plus the presence of hands which were broad and short in shape. The parents were distantly related, and the two youngest children were mentally defective.

Hanhart (1947) has described two special forms of palmo-plantar keratosis. The first is a regular dominant form with associated generalised lipomata; the second is a simple recessive form with feeble-mindedness and corneal changes. In both families showing the latter phenomena the parents were consanguineous. Hanhart proposes that the findings justify setting up an ectodermal syndrome based on a recessive inheritance expressed as disturbances of ectodermal cornification, as well as in homologous corneal lesions and arrested bodily and mental development.

An associated condition is that known as *keratoderma maculosa disseminata symmetrica palmaris et plantaris*, or *keratosis palmo-plantaris papulosa*. Small hard horny papules project up to 2 m. m. above the palmar and plantar skin surfaces, commencing after puberty. The first case described by Davies-Colley (1879) was in a Hindoo-Brahmin of 45, who was epileptic and an idiot.

ANHIDROTIC ECTODERMAL DYSPLASIA

This is a rare syndrome characterised by hypotrichosis, absence of sweat glands, adontia or hypodontia, and a characteristic facies. About 80 such cases are described in the literature, and Osbourn (1952), in presenting the fifth case also showing absence of breasts, published a typical photograph of his patient.

Generally there is only blonde sparse fine hair present, resembling lanugo, and eyebrows are absent. Skin is thin, pale, dry and sometimes scaly, and the prominent frontal bossing, depressed nasal bridge and thick protruding lips resemble those features as seen in congenital syphilis.

In a patient suffering from ectodermal dysplasia, Thannhauser (1936) found signs of adrenal medullary insufficiency (which is of ectodermal origin) and exostosis of the inner table of the skull (which arises from the mesoderm).

West (1937) described a family in which a man's first wife had normal children and grandchildren, but his second wife gave birth to five out of six children apparently suffering from the condition. He noted that they were also "shy and backward". A single case has been

described in Mongolians by Coello (1943) in which the Chinese man concerned had little hair, lacked sweat glands and several teeth and was mentally defective.

Falconer (1929) states that inferior mentality has been recorded in several of the cases, and Cockayne (1933), in referring to the sex-linked recessive form, says that the majority were of good intelligence but that several were dull.

The best study of anhidrotic ectodermal dysplasia and its association with mental deficiency is that of Halperin and Curtis (1942). They described a further case from a family of four in which another child with the defect had died, and two were normal. Their 14 year old patient showed the typical features and had a Binet I. Q. of about 50. A maternal grandfather had shown an ectodermal defect of the nails. The authors state that most commonly the condition is transmitted as a recessive sex-linked character, and rarely by a gene with incomplete dominance. They analyse 66 published cases and classify the intellect as follows:- Defective 1; inferior 17; average 20; superior 1; unspecified 27. Halperin and Curtis conclude that the gene for ectodermal dysplasia has a depressing effect upon the intelligence, and believe that this is not surprising in view of the ectodermal origin of nervous tissue. They believe that if it can be established that numerous syndromes of this nature in mental deficiency are the expression of unfavourable genes, a greater accuracy in classification of mental deficiency will result.

Penrose (1949) concludes that in this condition it is not yet known how many clinical and genetic entities are involved.

XERODERMA PIGMENTOSA (Kaposi's Dermatitis)

This disease of the skin has also been found in significant association with mental deficiency. At birth the skin appears normal, but inflammation appears with exposure to sunlight. The child develops photophobia within a few weeks of birth, and the conjunctiva and exposed skin become red. Freckles appear on the erythematous areas and, later, atrophic pits and telangiectases. Often epitheliomata or sarcomata develop; sufferers are said rarely to attain the age of 40, and Gates (1946) states that two-thirds die before the age of 15.

Xeroderma pigmentosa is transmitted by a recessive gene, and there is evidence of incomplete sex linking according to Gates and others.

Associated conditions include adherent ear lobes (Gates, 1946), infantilism and dwarfism (Elsasser et al, 1950), and these authors and Cockayne (1933) also list mental deficiency, the latter mentioning cases described by five authors.

The term Xerodermic Idiocy was first used by de Sanctis and Cacchione (1932) when they described three brothers aged 11, 7, and 6 suffering from the condition. The picture of typical pigmented xeroderma was associated with retarded bodily and mental development, impaired speech and testicular hypoplasia. The parents were healthy but were first cousins. Post mortem examination of the brain of one of the brothers showed neuroglial proliferation suggestive of senile changes, and the authors postulated some disturbance of ectodermal structures leading to premature degenerative changes.

Another good description of cases of xerodermic idiocy is that of Silberstein (1938) who found the condition in brothers aged 13 and 12.

The skin lesions were associated with a slurred and explosive type of speech, a slightly spastic gait and marked mental deficiency. The genital glands were normal and the possibility of some associated hypothyroidism was suggested by a lowered B. M. R. in one case, and slight delay in ossification of carpal bones. Silberstein postulates the possibility of a degenerative condition of the central nervous system analogous to the degenerative lesions of the skin. In reviewing the literature he found six reported cases of xeroderma pigmentosa with idiocy.

An up to date review of the subject is that of Elsasser et al. (1950) who find that in one seventh of all cases of xeroderma pigmentosa there is associated infantilism or dwarfism, and in some instances idiocy, endocrine hypofunction, and certain neurological changes are found. They describe a boy of 16 with pituitary dwarfism, abnormal porphyrin metabolism, idiocy, xeroderma pigmentosa and a benign fibromatous growth of an eye. The neurological picture was similar to that of Friedreich's ataxia, and one brother was similarly affected. The authors believe that the syndrome is due to a developmental disturbance of the primitive neural canal involving the pituitary, and that a metabolic factor is responsible for the photosensitisation of the skin.

MONILETHRIX

This condition will be briefly mentioned as it is apparently also an ectodermal dysplasia, and two affected boys recorded by Polland (1912) were mentally defective. The characteristics are a beaded appearance of individual hairs and keratosis follicularis. It appears to be a simple dominant (Gates, 1946) and shows a partial linkage with dark hair. All the hair may be affected or it may occur in patches accompanied by baldness or thin hair.

IMPLICATIONS FROM THE ABOVE FACTS

From the literature which is reviewed in the preceding pages it appears that there are several syndromes in which ectodermal dysplasia is associated with mental deficiency. The point has already been made that the skin and nervous system both arise from the developmental ectoderm. Therefore, various authors have not been surprised to find developmental disorders of the one structure associated with developmental disorders in the other.

It has also been suggested by various writers (e. g. Halperin and Curtis, 1942) that there is a possibility that syndromes involving mental deficiency have not yet been adequately studied and that new associations remain to be discovered.

It seemed reasonable, therefore, to study the incidence of ectodermal disorders in mental defectives and compare this with the incidence in non-mental defectives. The results of such a study should confirm or dispute the theories propounded above.

The clinical work in this paper concerns such a study. Before describing this I will refer briefly to other workers' papers on the incidence of skin diseases in various groups. I have been unable to find any paper in which a group of mental defectives was compared with a group of normal individuals, but separate studies of each group have been done.

INCIDENCE OF DYSKERATOSES AND ECTODERMAL DYSPLASIAS IN THE GENERAL POPULATION

In general, the textbooks on dermatology tend to describe certain conditions as common and others as rare. Such books make it plain that

the authors regard the various manifestations of dyskeratosis as being rare, although no actual figures of incidence are given.

In two recent studies Zakon et al. (1948 and 1949) investigated the incidence of skin disorders. This was in order to determine which conditions were the more common so that emphasis might be placed on teaching these to medical students. Of 1,065 patients seen in private dermatological practice there were two cases of keratosis pilaris, two of dyshidrosis and two of keratosis follicularis. Of 1,000 cases attending a dermatological clinic there were eight cases each of ichthyosis and dyshidrosis, four of xerosis, two of keratosis palmaris et plantaris and one of keratosis pilaris. It should be noted that the incidence (of 0.8%, for example, in the case of ichthyosis) is not that in the general population, but of all cases seeking dermatological advice.

Another study of the incidence of dermatoses in infants and children attending a skin hospital was reported by Perlman (1953). Out of a total of 967, the following conditions, pertinent to the present paper, were found:- ichthyosis, 3 cases; xeroderma 3; dyshidrosis 1; vitamin A deficiency 1; keratosis palmaris et plantaris 1; congenital dystrophy of nails 1.

Of course it is possible that patients suffering from mild xerosis or ichthyosis might never seek advice or might never attend a dermatologist, however it does seem likely that these diseases are indeed rare.

I have been unable to find any study of the incidence of such diseases in the population at large.

INCIDENCE OF DYSKERATOSES AND ECTODERMAL DYSPLASIAS
IN MENTAL DEFECTIVE POPULATIONS

I have found no studies in which mental defectives were examined specifically for these conditions, but two general papers on skin diseases in mental defectives must be mentioned.

Butterworth and Wilson (1938) examined the incidence of skin diseases in a feeble-minded population of 1,895. As many as 68 different dermatological diagnoses were made in this group, but unfortunately the authors detailed only the more frequent conditions plus some that aroused special interest. They found 153 examples of acne, naevi in 140 patients, hypertrichosis in 17, marked hypotrichosis in one man, neurofibromata in 5 patients, adenoma sebaceum in 6 and café au lait spots in 55. The results of trauma were noticed in 30 cases, including areas of hyperkeratosis due to chronic self-inflicted bites. If other forms of dyskeratoses were noticed they were apparently not considered important enough to warrant mention.

A study by Touraine (1947) deserves fuller review, because it covers a similar field to the present paper. Touraine examined the skins of 171 mental defectives in France, and he limits his paper to the cutaneous dysplasias associated with different degrees of oligophrenia. He concludes that there are no specific morphological types of mental defectives as regards the constitution of the hair (form and colour), eyes, teeth, height, etc. Naevi are no commoner than in the general population, but the hereditary skin diseases are relatively more frequent in oligophrenia. He believes that this is especially true in cases of the rarer diseases such as hypohidrosis, acanthosis nigricans in juveniles with obesity, koilonychia, etc. Unfortunately he

seems to base his conclusions on clinical impression, or at least he makes no mention of a control study of members of the non-mental defective population.

Touraine defines four groups of skin disorders associated with oligophrenia: -

(1) Symptomatic skin disease, due to the presence of oligophrenia. For example the effects of hair pulling, biting, etc.

(2) Secondary oligophrenic ectodermoses in which the mental deficiency and skin disorders are each secondary to a common cause.

The cause may be endocrine or metabolic:

(a) Endocrine - he instances changes associated with pituitary disorders such as acromegaly, arachnodactyly, Frohlich's syndrome, etc. Thyroid hypofunction, causing cretinism and myxoedema, also affects the skin. Under the classification of mixed or obscure endocrine disorders he includes mongolism with loose soft skin, scrotal tongue, etc.

(b) Metabolic - here are included Neimann-Pick's disease, Gaucher's disease, gargoylism and other conditions.

(3) Primary oligophrenic ectodermoses in which both the skin changes and mental deficiency are due to a congenital disturbance of development (nearly always hereditary and familial). There is a long list of examples, under various subdivisions, which will be given only briefly here: -

(a) Hyperectodermoses - this includes conditions such as ichthyosis, palmo-plantar keratoderma, onychogryphosis, and Darier's disease.

(b) Anomalies of pigmentation - melanism; incontinentia pigmenti; dystrophia pigmentosa; neuro-cutaneous melanoblastosis.

(c) Anomalies of hair - hypertrichosis foetalis; hypertrichosis generalis; monilethrix.

(d) Congenital angioses - cuti marmorata telangiectica congenita; acrocyanosis with hypothyroidism.

(e) Hyperplasias of different tissues - cutis verticans gyrata; cutis hyperelastica; polydactyly, etc.

(f) New ectodermal growths - Recklinghausen's disease; tuberous sclerosis; Hippel-Lindau angiomatosis; Sturge-Weber (encephalo-trigeminal) syndrome.

(g) Hypoectodermoses - albinism; hypotrichosis; atrophic nails; anhidrosis; hypotrichosis and adontia; xeroderma pigmentosa, etc.

(h) Dysectodermoses - status dysraphicus; spina bifida; oxycephaly; cranio-facial dysostosis, etc.

(4) Touraine calls the final group the dysembryonic ectodermal oligophrenias. Unlike group (3), the cases in this group are rarely familial, as there is no genetic factor involved, but rather a disorganisation of the development of the egg or the embryo. Touraine believes that typical skin manifestations are the naevi of all types. He finds that such naevi are no commoner in mental deficiency than in the general population, and relates this to his belief that naevi are anomalies of development of the skin rather than of the primitive ectoderm before it has given rise to the nervous system.

It seems likely that much of Touraine's classification will require revision in the light of future knowledge. For example the four conditions listed under the primary oligophrenic ectodermoses (group (3) (f)

above) were originally grouped as phakomatoses by Van der Hoeve (1938). It has recently been claimed by Weber (1951) that Hoeve's phakomatoses are essentially of a naevoid nature.

As the whole subject is as yet a matter for debate on the part of the dermatologists, it seems likely that a final satisfactory classification of the "oligophrenic ectodermoses" must await further findings on the aetiology of these skin disorders.

THE PRESENT CLINICAL STUDY

For the purposes of the present clinical study it seemed most profitable to confine my attention to the cutaneous anomalies of keratinisation. As explained in the introduction, this is the field which has been least explored. Broadly speaking the term "dyskeratoses" covers the skin anomalies which were discussed in the earlier section of this paper. Strictly speaking, the conditions of xeroderma pigmentosa and monilethrix may not be classifiable as such, but no examples of these were found in any of my clinical studies. Throughout the remainder of this paper, therefore, the term dyskeratoses will be used to cover the anomalies which were found, such as ichthyosis and keratosis follicularis.

Although this is possibly a rather loose usage of the term, there is no general agreement among dermatologists as to what constitutes a "dyskeratosis". Hyman(1953) has criticised the way in which the term is used by others in reference to various skin diseases.

CLINICAL FINDINGS

So that the foregoing conclusions regarding the associations of dyskeratoses and oligophrenia might be tested, two sample populations of mental defectives were examined and compared with control groups.

All the population samples to be described were personally examined. During an early pilot study an attempt was made to establish definite clinical criteria for, say, the differentiation between keratosis pilaris and keratosis follicularis, or whether a case of ichthyosis was to be recorded as severe or mild. Such criteria were based on the descriptions in the literature which has already been reviewed, and, as these were rigidly adhered to, I feel that subjective factors on my part were minimal.

OLIGOPHRENIC GROUP 1

In November and December 1950 I examined all available patients in Gogarburn Hospital, Edinburgh, Scotland. These patients were all certified mental defectives, permanently resident in the hospital for varying periods of time.

Because of the implication of various authors that dietary factors are responsible for some of the dyskeratoses, this must first be briefly discussed.

All the patients were receiving the current British food rations. These were well supplemented by carefully chosen non-rationed foods including vegetables, and there was no reason to suspect that the available diet was deficient in any way. Kirman(1951) has pointed out that avitaminosis may develop due to inadequate intake in idiots who require spoonfeeding, and who may refuse all but a soft pappy diet. However,

careful inquiry was made of the nurses looking after the cases found to have dyskeratoses, and there was no evidence of inadequate intake of the available diet in any instance. In addition, no patient suffering from a dyskeratosis was found with any clinical evidence of malnutrition or avitaminosis.

A total population of 488 patients was examined (269 males, and 219 females), varying in age from 6 to 76 years: -

Children under 16 numbered 96; adults over 16 numbered 392.

Patients with mongolism numbered 14.

Patients with epilepsy numbered 96.

The following table gives details of the incidence in the total and in various sub-groups: -

	<u>Number with dyskeratoses</u>	<u>Percentage</u>
488 patients examined	59	12.0%
96 children under 16 years	2	2.0%
392 adults over 16 years	57	14.5%
269 male patients	36	13.3%
219 female patients	23	10.5%
14 patients with mongolism	6	42.8%
96 patients with epilepsy	9	9.3%

These figures exclude 2 cases of typical adenoma sebaceum associated with epiloia. In addition keratosis pilaris was found in 71 out of the total of 488 (14.5%); 18 cases in children under 16, 53 in adults.

Many of the cases of dyskeratoses showed a mixed picture. For

instance, ichthyosis and Darier's disease were often found together, and xeroderma and Darier's disease were also associated.

Full details of skin findings are given in Appendix I.

Taking into consideration what seemed to be the condition most markedly present, the following breakdown is obtained: -

Darier's disease	29
(keratosis follicularis)	
Ichthyosis	13
Xeroderma alone	14
Localised ichthyosis of knees and elbows, not accounted for by extraneous pressure (see later discussion)	1
Malformed nails	1
Scaly eczematous condition apparently associated with sensitivity to sunlight	1

Total	<u>59</u>

Four patients showed marked thickening of the skin of the knees and elbows, in addition to other evidence of dyskeratosis, and 1 patient (recorded in above table) showed this condition alone. In no instance was there any known occupational or habit pattern to account for this. (Various other patients who regularly scrub floors were found with hyperkeratosis of knees, but these were omitted from the present series.)

One case of xeroderma had a large angioma of the cheek.

One case of Darier's disease had been born without eyeballs (which are of ectodermal origin).

STATISTICAL STUDY OF THE INCIDENCE OF DYSKERATOSES IN MENTAL DEFECTIVE GROUP 1

The case notes of all 59 patients with dyskeratoses were studied. The most interesting feature to be discovered was that only two patients (nos. 58 and 59 in Appendix I) had been definitely recognised as secondary mental defectives. There was also a possibility that case no. 53 was secondary.

Tredgold (1947) tabulates the causes of amentia as follows: -

- (1) Amentia due to inheritance - germinal, intrinsic or endogenous. This is usually called primary amentia.
- (2) Amentia due to environment - extrinsic or exogenous. This is usually called secondary amentia.
- (3) Some cases may be due to a combination of (1) and (2).
- (4) Amentia without discoverable cause.

Tredgold finds approximately 80% primary and 20% secondary mental defectives in any sample, and most authors agree with these figures. Penrose (1938), however, finds only 38% definitely primary or secondary, the remainder being recognised as a result of both inheritance and environment.

From our knowledge of the apparent hereditary nature of the dyskeratoses it certainly would appear likely that these skin conditions would be more frequent in "primary" mental defectives. Patients falling into the "secondary" group can usually be classified as having mental deficiency due to traumatic, infective, degenerative or deprivative causes. From many points of view this dichotomous classification is an unsatisfactory one, and indeed other systems have been suggested. However, for our present purpose it is interesting to question the incidence of

dyskeratoses in these two classes. Certainly we might expect to find a lower incidence of dyskeratoses in cases which were clearly secondary in type.

However, it should be stated now that this paper will present evidence to suggest that some oligophrenias may be due to adverse intrauterine conditions. For example, it will be suggested that mongolism (which is usually classified as a primary amentia) may be due to environmental factors alone, during gestation, or (2) to environmental factors enhancing the pathological effect of a gene abnormality. In the first instance the mental deficiency would be strictly due to environmental factors before birth (therefore classifiable as secondary). In the second instance the disorder would be due to a combination of genetic and environmental factors. This last is indeed in accordance with the beliefs of Penrose (1951) who does not postulate the nature of the environmental factor. The present paper will suggest that a disorder of vitamin A metabolism may be this factor.

In practice, most workers who are classifying mental deficiency as either primary or secondary have looked for environmental factors (e. g. traumatic, infective, degenerative and deprivative). Finding evidence of such factors has led to classification of such cases as secondary. In the absence of such recognisable factors, cases have been regarded as primary. It seems clear that in the present paper we are interested to see if the dyskeratoses occur more frequently in cases where genetic or intrauterine factors are of aetiological importance. Such cases will be found in the group at present classified as "primary".

In the study of the Gogarburn Hospital mental defectives I only had the opportunity to examine in detail the files of the 59 patients with dyskeratoses. By the time I realised the desirability of knowing the classification of all the 488 patients, I was geographically far removed from the files. However, there is a mathematical means which will give us a good approximation of the total numbers in each classification.

In my study of the skins, I had examined a random sample comprising over 75% of the Gogarburn Hospital population. The Physician Superintendent had previously examined the same population to determine the classification of the patients (Bailey: personal communication, 1950). He found that the incidence of secondary oligophrenia in Gogarburn is 22%.

Applying this figure to the population that I examined gives the probable number of secondary cases as 108 (22% of 488). We can therefore assume that about 380 of my total of 488 suffered from primary amentia.

The following table expresses these findings: -

	With dyskeratoses	Without dyskeratoses	Total
Primary aments	56	324	380
Secondary aments	3	105	<u>108</u>
			488

Now we can examine these figures statistically by applying the null hypothesis. We may assume, for the moment, that the dyskeratoses are equally related to primary and secondary oligophrenia. With this in mind we may calculate X^2 (Chi-square) by comparing the expected

frequencies (e) with the observed frequencies (o).

The usual formula is :

$$\chi^2 = \sum \frac{(o - e)^2}{e},$$

but with a fourfold table a simpler method is applicable. The fourfold table can be stated as follows :-

	With dyskeratoses.	Without dyskeratoses	Total
Primary oligophrenics	56 (a)	324 (c)	380 (a+c)
Secondary oligophrenics	$\frac{3 (b)}{59 (a+b)}$	$\frac{105 (d)}{429 (c+d)}$	$\frac{108 (b+d)}{488 (a+b+c+d)}$

Here, Chi-square equals $\frac{(ad-bc)^2 (a+b+c+d)}{(a+b)(c+d)(a+c)(b+d)}$, where a, b, c and d are the cell numbers as in the above table.

Because the numbers involved are small in some instances, a more stringent formula was applied in the following statistical work. This formula tends to prevent any exaggeration of the value of Chi-square (Bradford Hill, 1950). Therefore, except where otherwise stated, the following formula has been used in the rest of this paper :-

$$\text{Chi-square equals } \frac{(ad - bc - \frac{1}{2}(a+b+c+d))^2 (a+b+c+d)}{(a+b)(c+d)(a+c)(b+d)}, \text{ when } (ad)$$

is the larger of the two cross products.

Application of this formula to the figures for primary and secondary oligophrenia gives :

$$\text{Chi-square equals } 8.09.$$

With this value, and with one degree of freedom (n = 1) it is seen from Fisher's (1936) tables that the probability (P) equals less than .01.

In other words, the observed difference in incidence of the dyskeratoses in primary and secondary oligophrenia would be unlikely to occur by

chance alone. Consequently, we may reject the hypothesis that the samples are drawn from a homogeneous population. Thus, there is evidence suggesting a significant relationship between dyskeratoses and oligophrenia of the primary type, as compared with the secondary type. The possible interpretation of this, and other, statistical conclusions will be reserved for the discussion.

By means of a similar statistical technique the occurrence of the dyskeratoses in males and females can be compared :

	With dyskeratoses.	Without dyskeratoses	Total
Males	36	233	269
Females	$\frac{23}{59}$	$\frac{196}{429}$	$\frac{219}{488}$

Here, Chi-square equals 0.690, and P lies between 0.50 and 0.30.

Thus, there appears to be only a chance relationship between the incidence of dyskeratoses in male and female mental defectives.

The occurrence of the dyskeratoses in patients with mongolism and epilepsy can now be considered. In each instance the subgroup of mongoloid and epileptic patients will be compared with the total population (488) less the number in the subgroup.

	With dyskeratoses	Without dyskeratoses	Total
Patients with mongolism	6	8	14
Patients without mongolism	$\frac{53}{59}$	$\frac{421}{429}$	$\frac{474}{488}$

Here, Chi-square equals 10.029, and P equals much less than 0.01.

It can therefore be asserted that there is a significantly higher incidence of dyskeratoses in patients with mongolism as compared

with the rest of the mental defectives.

	With dyskeratoses	Without dyskeratoses	Total
Patients with epilepsy	9	87	96
Patients without epilepsy	$\frac{50}{59}$	$\frac{342}{429}$	$\frac{392}{488}$

Here, Chi-square equals 0.541, and P lies between 0.50 and 0.30.

There is therefore no statistical significance in the different incidence of the dyskeratoses in the epileptic and non-epileptic mental defectives examined.

Finally, the incidence of the dyskeratoses in adult and child mental defectives can be compared.

	With dyskeratoses	Without dyskeratoses	Total
Adults	57	335	392
Children (under 16)	$\frac{2}{59}$	$\frac{94}{429}$	$\frac{96}{488}$

Here, Chi-square equals 10.118, and P equals less than 0.01. It can therefore be concluded that the difference in the occurrence of dyskeratoses in adults and children is of significance.

As already mentioned, conditions such as ichthyosis and keratosis follicularis appear to be regarded as relatively rare by authors of dermatology textbooks. Certainly, to find as many as 42 examples of these two conditions in a total population of 488 would seem to exceed expectations. Nobody, however, has given the actual incidence of these conditions, and it was therefore necessary to examine a control group.

CONTROL STUDY No.1

To determine if the total incidence of dyskeratoses was significantly higher in a mental defective population than in the general population a sample of 111 hospital cases was studied.

As far as possible it was desired to examine long term hospital patients whose diet might compare with the diet in Gogarburn hospital.

Some 90 per cent of the following cases had been hospitalised for at least three months. They were suffering from chronic orthopaedic diseases, poliomyelitis sequelae and the like, but apart from this were drawn from the general population.

Children under 16 years of age numbered 51.

Adults over 16 years of age numbered 60.

No case of keratosis follicularis or ichthyosis was uncovered, however 5 patients (3 children and 2 adults) had dryness of the skin and slight scaliness, similar to the condition in the oligophrenic group which was labelled "xeroderma."

In the case of the three children this xerosis was found on the arms, thighs and legs only; the two adults showed it on the trunk also.

Keratosis pilaris was found in 6 children.

Statistical comparison of Mental Defective Group 1 and ControlGroup No.1

	With dyskeratoses	Without dyskeratoses	Total
Mental defective group 1	59	429	488
Control group 1	$\frac{5}{64}$	$\frac{106}{535}$	$\frac{111}{599}$

Here, Chi-square equals 4.686, and P lies between 0.05 and 0.02.

Thus, we may regard the difference in incidence of the dyskeratoses in the mental defective and control groups as being of statistical significance.

It should be noted that the above significance is found when comparing the control group with the total mental defective group. If we were to compare the control group with the primary mental defectives (in whom the dyskeratoses occurred in 14.7 per cent of cases) the significance would be increased.

The above findings may now be summarised :-

- (1) In comparing a group of Scottish mental defectives with a control group it was found that the occurrence of the dyskeratoses was significantly greater in the mental defective group.
- (2) Among the mental defectives the dyskeratoses were significantly more frequently found in adults (over 16 years of age).
- (3) There is no significant difference in the incidence of the dyskeratoses between the sexes in mental defectives.
- (4) A significantly higher incidence of dyskeratoses (42.8%) was found in patients with mongolism.
- (5) The incidence of dyskeratoses in mental defectives with or without epilepsy was not significantly different.
- (6) There is evidence that the dyskeratoses are more frequently found in association with the types of mental deficiency at present usually classified as primary amentia.

THE SECOND CLINICAL STUDY

Although the findings of dyskeratoses among the Gogarburn group of mental defectives were significant in themselves, I welcomed the opportunity to compare further samples of oligophrenics and controls on the other side of the Atlantic.

This second study was carried out in North Carolina and includes a group of mental defectives (total 185), a sample of the general population (total 76) and a group of chronic hospitalised psychiatric patients (total 192).

The temperature and the humidity are high in North Carolina during the summer and I knew that the physiological need for sweating might mask some of the dyskeratoses. Because of this the hospitalised patients were examined exclusively during the winter months of 1952-53 and 1953-54.

OLIGOPHRENIC GROUP 2

This group consists of patients resident in the mental defective colony attached to the State Hospital at Butner, North Carolina. Patients are housed in temporary buildings at present, and were placed there because of crowded conditions in a State Training School. All the patients examined had been resident for over one year, and the majority were transferred five years ago.

These patients represent a selected sample of mental defectives inasmuch as only selected cases were transferred from the parent institution. These were patients considered to be unsuitable for further training, who could be easily managed and who were not bedridden.

I examined a random sample of these patients representing 61 per cent of the total population. In this sample I saw no high-grade feeble-minded patients. There was a low incidence of epileptics, and a relatively high incidence of men with congenital spastic disorders. Ages ranged from 17 to 75 years with a preponderance of patients in the age range 20 to 39.

Table I compares the age groups of the mental defectives and control samples. This shows that there were considerable differences in the age scatter in these groups under comparison. Such was inevitable with random selection of samples from these different populations. From our knowledge of the dyskeratoses it appears that these skin disorders are likely to remain once they have developed. The control groups showed a higher age incidence but a lower percentage of cases of dyskeratoses. If it is true that such skin disorders remain once they have developed, the differing age incidences would not be likely to invalidate the comparison. On the other hand, if a dietary deficiency is an important factor, it might be that fluctuations in the skin condition could occur. It was not possible to examine the records of each patient for evidence of such fluctuations. Some of the case histories of both mental defective and mental patients did record the presence of "dry scaly skin" in recent years. However, complete records of the physical condition throughout hospitalisation are not available. The State Hospital at Butner was opened only in 1947. All the mental defectives and most of the mental patients examined were transferred from other institutions. Even if such records had been available it is doubtful if they would have proved to be of much value. In my

TABLE I

	Mental Defectives		Control group 2a (general pop.)		Control group 2b (psychiat. pts.)	
	Males	Females	Males	Females	Males	Females
16 - 20 years	6%	1%	0%	5%	0%	0%
20 - 29	43	30	21	28	9	4
30 - 39	25	32	24	28	15	13
40 - 49	14	15	34	23	24	19
50 - 59	9	21	12	12	21	16
60 - 69	3	0	9	2	22	38
70 - 79	0	1	0	2	7	10
80 and over	0	0	0	0	2	0
Total no. of people examined	108	77	33	43	92	100

Table showing age scatter of compared groups of mental defectives
(group 2) and control groups 2a and 2b.

Figures are given as percentages to the nearest whole number.

TABLE II

	Mental defectives		Control group 2a (general pop.)		Control group 2b (Psychiat. pts.)	
	Males	Females	Males	Females	Males	Females
Under 20 years	0	0	0	0	0	0
20 - 29	4	4	0	0	0	0
30 - 39	5	3	0	0	1	0
40 - 49	2	2	0	2*	2	0
50 - 59	2	7	0	0	1*	0
60 - 69	2	0	0	0	3*	5
70 - 79	0	1	0	1	0	0
Total no. cases of dyskeratoses	15	17	0	3	7	5
Total no. of people examined	108	77	33	43	90	97

Table showing actual numbers of cases of dyskeratoses occurring in the various age groups of the three samples under comparison.

* An asterisk denotes that one of these cases showed evidence suggesting malnutrition.

Psychiatric patients who are basically mentally deficient have been omitted from this table.

experience, many examiners, while mentioning the presence of "dry, scaly skin", do not record the exact detail required in a study of the present type.

The incidence of the dyskeratoses at the various ages in each compared group is shown in Table II. In the case of the mental patients, I have excluded those who were known to be mentally deficient before onset of the psychosis. Examination of this Table shows no significant trend. The tendency for the dyskeratoses to occur in older persons in the control groups runs parallel to the actual age scatter in these groups, as shown in Table I.

Before proceeding to report the incidence of the dyskeratoses I must discuss the occurrence of localised xeroderma. This was found to be not uncommon in the hospitalised patients. Typically it occurred on exposed skin and was commoner in females. The actual incidence was as follows: -

Mental defective	males	9.2%
"	" females	37.6%
Psychiatric	males	13.0%
"	females	39.0%
General population	males	6.0%
"	" females	9.3%

These figures show that the condition is by far commonest in the hospitalised female patients. It should be pointed out that all the hospitalised patients were examined in winter time, whereas the general population sample was examined at any time of the year. The condition was observed in non-hospitalised persons only during the winter months,

however this number is small and it seems unjustified to attempt to consider this fact as necessarily significant. Nevertheless, if a climatic factor is involved, this might explain the lower incidence of the condition in the general population.

In women patients the xerosis was most marked over the fronts of the legs below the knees. In men it occurred most often on the arms below the elbows, however in 5 men (all over 55 years of age) it was also found below the knees.

None of the mental defectives or the male patients could offer me any information about this condition. However, many of the women mental patients stated that this dryness of the skin was only present during the cold winter months. Several others attributed the condition to various brands of soap.

The xerosis did appear in most cases to be confined to areas which are exposed to the weather. Most of the women were wearing nylon stockings which would not seem to give much protection. It is not clear, however, why men should suffer from the condition on the legs. Of the 5 men whose lower legs were affected, 3 were wearing long underclothes as well as thick trousers. In these instances, of course, a lack of exposure to fresh air might be a factor.

I can only conclude that this xeroderma of the distal halves of the limbs may involve climatic, dietary and environmental factors, including the factor of personal hygiene.

When this localised type of xeroderma was found it was not recorded as a dyskeratosis for the purpose of the present study. Cases recorded

as suffering from xeroderma all showed the condition in generalised form, with or without other disorders being present as detailed in the Appendices.

It should be added that examples of localised xeroderma were also seen in the British cases examined. Unfortunately I kept no records of this because such cases were not being recorded as having a dyskeratosis.

Incidence of Dyskeratoses in Oligophrenic Group 2

Of 185 patients examined 32 were found to have a dyskeratosis present. I had already met with the important question of the incidence of these skin disorders in primary and secondary oligophrenias. This time, therefore, I studied the patients and the clinical records in all cases to determine the classification.

The following table details the incidence in the total and in various sub-groups: -

	No. with dyskeratoses	Percentage
185 patients examined	32	17.2%
108 male patients	15	13.8%
77 female patients	17	22.0%
22 patients with mongolism	12	54.5%
10 patients with epilepsy	2	20.0%
133 primary mental defectives	30	22.5%
52 secondary mental defectives	2	3.8%

At this point it may be interesting to compare this mental defective group with the Scottish one. It is not permissible to compare the overall incidence of dyskeratoses in both groups because the United States

one has no children in it. The selected nature of the latter group has already been mentioned. For instance, there is a higher incidence of secondary mental defectives than would be expected - 28.1% as compared with the figure of about 20% stated by Tredgold. This is particularly marked in the male group where the figure is 33.3%. The explanation of this is that many mental defectives with congenital spastic disorders were selected for transfer to the Colony at Butner.

The apparently high incidence of dyskeratoses in patients with epilepsy will not be subjected to statistical scrutiny because actually only 2 cases (one of them an example of Rud's syndrome) are represented out of a small total of 10 epileptics.

The following table shows some comparisons between the Scottish and American mental defective groups concerning the incidence of the dyskeratoses. The values of Chi-square (calculated from the fourfold tables) are indicated, as are the values of P.

	Scottish	American	Chi-square	P
Adults with dyskeratoses	14.5%	17.2%	0.535	.30 - .50
Patients with mongolism and dyskeratoses	42.8%	54.5%	0.116	.70 - .80
Primary aments with dyskeratoses	14.7%	22.5%	3.774	Greater than .05
Secondary aments with dyskeratoses	2.7%	3.8%	0.015	.90

From these figures it can be seen that none of these differences is clearly statistically significant. However, the comparative incidence of dyskeratoses in primary amentias in the two countries almost reaches the 5 per cent level of significance.

There is a trend towards a higher incidence of the dyskeratoses in the American group and it can be concluded that these two groups are not entirely homogeneous as regards these skin disorders. However, there is no clear statistical significance in the different incidence which exists.

When the control groups in Britain and the United States are compared, no significant difference is found in the incidence of the dyskeratoses (Chi-square equals 0.053; P is approximately 0.80).

The skin conditions seen among the American mental defectives were of mixed type, as was seen in Scotland. Appendix 2 gives brief details of individual cases.

One of the two recognised cases of secondary oligophrenia with dyskeratoses (no.4 in Appendix 2) was a cretin who showed a generalised xeroderma. This was unalleviated by thyroid. (There were two other treated cretins, both with skins clear of disease).

Taking into consideration what seemed to be the condition most markedly present, the following breakdown is obtained: -

Xeroderma alone	19
Keratosis follicularis	7
Ichthyosis	<u>6</u>
	32

Compared with the Scottish group, this group showed a tendency for a greater occurrence of generalised xeroderma alone.

STATISTICAL STUDY OF THE INCIDENCE OF DYSKERATOSES
IN MENTAL DEFECTIVE GROUP 2

There seems to be a considerable difference between the incidence of dyskeratoses in males (13.8%) and in females (22.0%). However, 36 of the 108 males, and only 16 of the 77 females had a secondary type of oligophrenia.

The actual occurrence of dyskeratoses in cases with primary oligophrenia should therefore be stated: -

	With dyskeratoses	Without dyskeratoses	Total
Females with primary oligophrenia	16	45	61
Males with primary oligophrenia	<u>14</u>	<u>58</u>	<u>72</u>
	30	103	133

Application of the formula (already given) to these figures shows that

Chi-square equals 0.525.

This figure indicates that such a difference in incidence might occur by chance in from 3 to 5 samples out of every 10. It can therefore be stated that there is no significant difference in incidence of dyskeratoses in males and females with primary oligophrenia in the present sample. This is in accordance with the Scottish findings.

Now, the incidence of dyskeratoses in primary and secondary mental defectives will be compared: -

	With dyskeratoses	Without dyskeratoses	Total
Primary oligophrenics	30	103	133
Secondary oligophrenics	<u>2</u>	<u>50</u>	<u>52</u>
	32	153	185

From these figures Chi-square equals 7.887, and P is less than 0.01. It can therefore be stated with considerable confidence that this group of mental defectives shows a significantly higher incidence of dyskeratoses in patients with the primary type of deficiency (as was shown also in the Scottish patients).

The incidence of dyskeratoses in patients with and without mongolism is shown in the following table: -

	With dyskeratoses	Without dyskeratoses	Total
Patients with mongolism	12	10	22
Patients without mongolism	<u>20</u>	<u>143</u>	<u>163</u>
	32	153	185

Here, Chi-square equals 21.351, and P equals much less than 0.01. This figure shows an extremely significant statistical relationship between mongolism and the dyskeratoses as compared with the incidence of the skin condition in the group without mongolism. Again, this finding is in accord with the Scottish one.

CONTROL STUDY NO. 2a

To compare the incidence of the dyskeratoses in mental defectives and non-mental defectives I endeavoured to examine a group of the "normal" general population in North Carolina. Many difficulties are inevitably encountered when one attempts to select a random sample of healthy subjects for physical examination. I did not succeed in overcoming these difficulties and, as a result, my sample is small and subjects were not selected totally at random. My subjects were necessarily persons who were known to me. They consist in the main of a group of hospital workers

and a number of ambulant psychiatric patients who were not hospitalised (at least up to the time of examination).

Total subjects examined	76
Males	33
Females	43

The age distribution has already been shown in Table I. In general, the ages are closer to those of the North Carolina mental defectives than are the ages of the psychiatric patients to be described as Control Study No. 2b.

A total of 3 instances of dyskeratotic skin disease were noted (all instances of mild xeroderma). Details are recorded in Appendix No. 2a. In 2 of the persons with dyskeratosis the skin condition may have been due to malnutrition and hypothyroidism respectively. However, I have not eliminated these figures from my calculations. All 3 examples occurred in women, but with the small numbers involved it is useless to attempt to find any significance in this fact.

CONTROL STUDY NO. 2b

In this study I examined 194 chronic psychiatric patients who were selected at random from the chronic population in the State Hospital at Butner. Certainly this is not a "normal" group to compare with the mental defectives, but I have taken care to ensure at least that it is not a mental defective group.

Apart from giving me a larger sample for comparison purposes, I was interested in this group from the dietary point of view. Patients in both the mental hospital and the mental defective colony are presented with exactly the same food which is prepared in a central kitchen. If dietary factors are significant (in causing many of the instances of dyskeratoses in mental defectives) we might find a similar incidence of

such skin disorders in non-mental defectives who eat the same food.

All of these patients eat in self-service cafeterias. A few of the mental defectives have to have their trays carried for them, and those who require it are spoon fed. In general I found that the mental defectives were better supervised at meals than the psychiatric patients. The possibility of avitaminosis might therefore seem to be more likely in the psychiatric group. In the latter group I saw 2 patients (nos. 4 and 9 in Appendix 2b) who did seem to have a mild degree of malnutrition. In neither group, however, did I see any patient with any of the recognised gross clinical signs of avitaminosis (if we assume that the dyskeratoses themselves are not such a sign).

The hospital diet is a carefully controlled one and appears to be adequate in all respects. I was particularly interested in the dietary content of fats and vitamin A because of suggestions that lack of one or the other of these might be a factor in the production of certain dyskeratoses.

The hospital dietician supplied me with the following figures, contained in the average cooked food supplied daily per person in the middle of 1953: -

Calories	2818
Fats	98 Gm.
Vitamin A	7833 i.u.

Since that time the kitchen facilities have been increased, and for February 1954 the figures are: -

Calories	3090
Fats	98.3 Gm.
Vitamin A	10,284 i.u.



These amounts would appear to be entirely adequate. As regards vitamin A, the recommended daily allowance for an active man of 70 Kg. or a woman of 56 Kg. is said to be 5,000 i.u. (American Medical Association, 1941).

Relatively mild degrees of avitaminosis A have been found in United States Populations by various workers. For instance, Kruse (1941) found ocular lesions (considered to be due to avitaminosis A) in 49 per cent of members of a low income group. Again, Jeans and Zentmire (1936) detected impaired dark adaptation in from 26 to 79 per cent of children from different social groups. On the other hand, fully developed xerophthalmia is stated to be extremely rare in the United States (McLester, 1949).

One special study deserves mention here, as it was done at Duke University which is only 15 miles from the State Hospital at Butner and which draws on a very similar section of the North Carolina population. Callaway et al. (1945) performed a dietetic survey on 354 patients attending the dermatological department of Duke Hospital. They found nutrition to be good, diets satisfactory and plasma vitamin A levels normal. All these factors compared favourably with control cases in the same region. These workers concluded that dietary factors were not important in skin disorders, and, incidentally, their figures included 5 patients with ichthyosis all of whom had normal levels of plasma vitamin A.

In the case of the groups under present consideration it seems clear that adequate dietary vitamin A is available. However, it was not possible to estimate how much of the available diet is actually eaten on an average

by individual patients. Similarly, we know nothing of the percentage of vitamin A actually absorbed after ingestion or of the amount successfully utilised in metabolism.

It can only be stated that the average patient in these groups would have to refuse from one third to one half of the vitamin A-containing foods before an inadequate intake might be reached. Further study of this question is recommended at the end of this paper.

Details of the psychiatric patients examined

	No. with dyskeratoses	Percentage
194 patients examined	17	8.7%
94 males	9	9.5%
100 females	8	8.0%

The age incidence of all patients and of patients with dyskeratoses has been shown in Tables I and II. Of the 94 male patients examined 2 were excluded as they had been hospitalised for less than one year.

Of the 9 men showing a dyskeratosis, 2 cases (nos. 2 and 6 in Appendix 2b) will be excluded from statistical consideration as they are known mental defectives and it is intended to obtain a group of non-mental defectives for comparison purposes.

The final statement, therefore, is that of 90 non-mental defective males, 7 showed dyskeratoses. This figure 7 includes 2 patients (nos. 4 and 9 in Appendix 2b) who seemed to have a mild degree of malnutrition secondary to another cause.

Of the 100 female patients there were 8 cases showing dyskeratoses (xeroderma only). However, a study of the case histories revealed that

3 of these 8 patients were known to be mentally defective before the onset of the psychoses (nos. 11, 12 and 13 in Appendix 2b). These 3 patients have therefore been excluded from the final figures which now show that in 97 female patients there were 5 examples of dyskeratoses.

It has already been pointed out that this group of females showed the highest age incidence of all the groups (Table I). I observed in this group the highest incidence of loose and inelastic skins of senile type.

The final figure for the incidence of dyskeratoses in group 2b is 12 out of 187 male and female psychiatric patients.

Statistical comparison of mental defective group 2
and control groups 2a and 2b

	With dyskeratoses		Without dyskeratoses		Total
Mental defectives (group 2)	32	(19.4)*	153	(165.6)	185
Control group 2a	3	(8.0)	73	(68.0)	76
Control group 2b	<u>12</u>	<u>(19.6)</u>	<u>175</u>	<u>(167.4)</u>	<u>187</u>
	47	(47.0)	401	(401.0)	448

* Figures in parentheses are calculated expected numbers (see text).

These figures can be conveniently examined by stating the null hypothesis - that the incidence of dyskeratoses in any group occurs purely by chance. The expected values (e) in each cell are calculated by the hypothesis of independence, and these are shown in parentheses in the same table.

Then, Chi-square equals $\sum \frac{(o - e)^2}{e}$ which, here, equals 15.89.

With this table, n equals 2, and therefore a Chi-square of this value shows a probability of less than 0.01. We can therefore reject the hypothesis that the dyskeratoses occur purely by chance in the above groups.

Comparing the mental defective sample and the sample of the general population (group 2a) gives the following fourfold table: -

	With dyskeratoses	Without dyskeratoses	Total
Mental defectives	32	153	185
Control group 2a	<u>3</u>	<u>73</u>	<u>76</u>
	35	226	261

Here, Chi-square equals 7.158, and P is less than 0.01. This means that there is less than 1 chance in 100 that the different incidence of dyskeratoses (in the mental defectives as compared with the non-mental defective group 2a) is merely due to chance alone.

Comparing the mental defective sample and the sample of psychiatric patients (group 2b) gives the following fourfold table: -

	With dyskeratoses	Without dyskeratoses	Total
Mental defectives	32	153	185
Control group 2b	<u>12</u>	<u>175</u>	<u>187</u>
	44	328	372

Here, Chi-square equals 9.538, and P is less than 0.01. Again, it is extremely unlikely that the dyskeratoses are distributed only by chance among the mental defectives and the non-mental defective controls.

Finally, comparing the two control groups with each other gives the following table: -

	With dyskeratoses	Without dyskeratoses	Total
Control group 2a	3	73	76
Control group 2b	<u>12</u>	<u>175</u>	<u>187</u>
	15	248	263

Here, Chi-square equals 0.238, and P lies between 0.50 and 0.70. It is clear, therefore, that there is no significant difference in the occurrence of the dyskeratoses in the two control groups.

It may also be mentioned that, as was to be expected, Chi-square has a value of 15.61 (P therefore, equals less than 0.01) when the mental defectives (group 2) are compared with the amalgamated groups (2a and 2b) using the fourfold table.

It can be concluded that, in the North Carolina group of mental defectives, the findings are in accordance with the Scottish ones. In particular, the highest incidence of dyskeratoses is significantly found in mongolism. A significantly higher incidence of dyskeratoses occurs in primary as opposed to secondary oligophrenia. Also, the mental defectives as a whole show a significantly higher incidence of the skin disorder than in the control groups.

Amalgamation of all the mental defective figures (Scottish and American) shows the following: -

	Total	No. with dyskeratoses	Percentage
All mental defectives examined	673	91	13.5%
Primary mental defectives	513	86	16.7%
Secondary mental defectives	160	5	3.1%
Patients with mongolism	36	18	50.0%

The above figures are for all examples of dyskeratoses. It should be pointed out that the majority of control group subjects who had dyskeratoses (20 in all) suffered from generalised xeroderma only. Only 4 examples of dyskeratoses of other type were seen. Among the mental defectives, on the other hand, there were 33 examples of xeroderma alone and 58 examples of other types of dyskeratoses.

Of the 374 non-mental defective controls examined on both sides of the Atlantic, 20 showed a dyskeratosis. This gives an incidence of 5.3 per cent, whereas the incidence in all the secondary mental defectives was only 3.1 per cent. However, from these figures Chi-square is calculated to equal 0.792, and P lies between 0.50 and 0.30. Thus, the difference in incidence in controls and secondary mental defectives is such as might easily have occurred by chance, and is not statistically significant.

THE SYNDROME OF RUD

During 1949 I discovered a patient suffering from this syndrome, in which the cardinal symptoms are oligophrenia, epilepsy and ichthyosis. As only five cases had been previously described in the literature, I studied this patient in some detail, and am reporting the case here for the first time. In addition, I came across another 3 examples during my routine survey of the Gogarburn Hospital patients and 1 example among the North Carolina patients.

Case No. 1

On 3/5/49 Richard S., aged 19, was admitted to Cherry Knowle Hospital, Sunderland, England, in an ataxic and confused condition. He was said to be epileptic, and had been brought from his home by the Police, who were told he was having violent outbursts. On being stripped for bathing, the most notable feature was that his skin appeared almost black in places. This was due to a severe ichthyosis.

Within the next few days the patient's mental condition improved. For six days he was mute; then he showed disorientation, confabulation and perseveration, all of which gradually cleared. Within 14 days he was sufficiently lucid and volitional to become a voluntary patient.

From the time of his admission he experienced both major and minor epileptic attacks, and although much improved, he remains institutionalised.

Mental State.

Having recovered from the acute mental confusion from which he suffered on admission, and which appeared to be an epileptic furor, he was found to be mentally deficient.

The early clinical picture did resemble a toxic-confusional psychosis, and may have been due to drugs or some intercurrent infection. The only known administration of a drug was a single injection of a barbiturate before his admission to hospital. Examination failed to reveal any evidence of infection. I have been inclined to regard the violent outburst which occurred at home as being incidental to his epilepsy. The barbiturate may have contributed to the clouding of consciousness, but the psychotic features were evident for rather longer than one would expect from a single injection, and were therefore probably also secondary to the epilepsy.

He is feeble-minded, can barely read or write, but is well occupied in the occupational therapy department at simple tasks. At times he is inclined to be mischievous and to interfere with other patients, and he has impulsive outbursts, usually before epileptic attacks. He is easily pleased by a few words of praise, and in general is like other feeble-minded epileptics.

His mental age is 7 years, by the Terman Merrill revision of the Stanford-Binet Intelligence Scale.

The epileptic attacks have been typical *grands mals* and *petits mals*. In the week following admission the patient had several *petits mals* and one *grand mal* seizure on most days. The major seizures were reduced in frequency by administration of phenobarbitone and phenytoin, and the minor attacks responded well to Tridione. Now, seizures occur as infrequently as once per month.

Physical condition: No abnormalities are to be found in the cardiovascular, respiratory or nervous systems. The ataxia, which was present on admission, rapidly cleared up, and was probably due to the injection of a barbiturate.

The skin shows a severe ichthyosis; in parts the thickened epidermis forms patches like a snake's skin. The condition is most marked over the trunk and the proximal parts of the limbs. At all times the skin feels dry and scaly, and only in hot weather has any axillary sweating been noticed. Administration of full doses of vitamins (especially of vitamin A) and later of thyroid has had no influence on the ichthyosis. The skin is kept most supple and free from cracks by the application of vaseline or lanolin following bathing.

The blood picture and cerebro-spinal fluid are normal in all respects. Radiography of the skull reveals normal bone structure, including the sella turcica, and when I performed pneumo-encephalography I was able to demonstrate the presence of normal sized and shaped ventricles, and no cortical atrophy.

The teeth show a moderate degree of the hypoplasia of the enamel described in mental defectives by Spitzer and Mann (1950).

The external genitalia are average in size, but the secondary sex characters are not well marked. Pubic hair is poorly developed and shows no definite tendency towards a male distribution. Beard hair grows slowly, and his voice is high pitched. He is of a timid disposition, and one of his nurses describes him as "girlish".

Personal History:

Patient was born at full term following a normal delivery, and appeared to be a normal baby. His mother noticed the dryness of his skin at about 1 year of age, but otherwise his infancy was uneventful. Definite scaling of the skin began at about the age of 5 years.

A report from his school describes him as "weak natured and of poor intelligence", and for a time he attended a special school for the educationally subnormal.

He left school at the age of 14, and obtained simple work in a factory where he was first seen to have a major epileptic convulsion. His mother is not aware of his having had attacks before this age, but from that time they were frequent and his work record was poor.

Family History:

Patient is the fourth in a sibship of six (3 males and 3 females). His siblings are all of average intelligence, and free from ichthyosis and epilepsy. Two of the patient's sisters are married, but have had no children as yet.

His parents were not consanguineous. The father had been a labourer who died at the age of 52 from a chest complaint, and the mother is alive and well, aged 52.

The family tree has been traced back for three generations, but no instance of mental deficiency, epilepsy, or skin abnormality was brought to light.

Case No. 2

This is the case cited as patient No. 26 in the Gogarburn survey (Appendix No. 1). M. B. is a 20 year old feeble-minded girl who was certified as a mental defective at the age of 12, and has been resident in Gogarburn Hospital since that age. Her I. Q. is 63 (Terman-Merrill) and she suffers from severe epilepsy, having an average of three major seizures weekly. She is an aggressive girl who has made frequent attempts at escape. Although she is well developed and shows no evidence of hypogonadism, she is of small stature.

The skin of the whole trunk is xerodermic, ichthyosis is marked on the legs and thighs, and in the latter position there is an additional

keratosis follicularis. The arms and shoulders show a marked degree of keratosis follicularis and a xerosis which in places amounts to patches of ichthyosis.

The patient is illegitimate, being born of a 40 year old father and a 20 year old mother. The mother is also feeble-minded, and is also a Gogarburn patient. The father is said to have been very bad-tempered and addicted to alcohol. The maternal grandmother is known to have been of subnormal intelligence.

The history mentions that the patient is said to have had an accident to the head in childhood and that the fits came on a year or two later. However there is no evidence that any actual damage was sustained if such an accident occurred, and it seems apparent that the mental deficiency is of familial type.

The nurses who have known this girl over the past eight years report that her skin has always been dry, scaly, and covered with prominent "goose-pimples" in places.

This patient has a brother who is also a certified mental defective in Gogarburn Hospital. He is case No. 51 in appendix No. 1, and was also illegitimate. Aged 17 at the time of examination, the brother is feeble-minded, and has been a patient for 5 years. He has not suffered from epilepsy up to the present, but has a mild xerodermic process over the whole body, which is most marked on the arms and legs, where pronounced scaling is seen. He shows normal axillary sweating, the body hair is poorly developed, the genitals are small, and he is of small stature.

Case No. 3

This is case no. 8 in Appendix no. 1.

M. J., a 62 year old female imbecile has been in hospital for 8 years. She suffers from occasional epileptic seizures. The admitting doctor noted that the skin was "very dry, patchy and scaling". At the time of my examination she had a mild generalised ichthyosis. She has talipes equinovarus. There is no evidence of hypogonadism, and no family history is known.

Case No. 4

This is case no. 30 in Appendix no 1.

M. T., a feeble minded female aged 51 has been in hospital for 26 years. She suffers about one grand mal epileptic seizure each month. At the time of my examination the skin showed a generalised xeroderma with areas of considerable scaling. There was no evidence of hypogonadism. Unfortunately the family history is not known.

(Although this case does not show a fully developed ichthyosis of the severity shown in the first three cases, the xerosis is marked. This patient presents a similar skin picture to that in the case presented by Stewart (1939) as a case of Rud's syndrome, and is therefore included in the present series.)

Case No. 5

This is case no 26 in Appendix no. 2.

M. M. is a female imbecile, aged 39, who suffers from epilepsy, being one of the patients whom I saw in North Carolina.

Her father (who is "almost blind") was aged 33 at the time of her birth, and her mother was aged 30. The mother deserted her children

while the patient was still young, and is said to have been "illiterate and feeble-minded."

The patient comes from a sibship of 8, being herself the fifth child. The siblings are said to be "apparently normal."

She is stated to have had convulsions at the age of 2 months and to have suffered from measles in infancy. She did not attempt to walk until after the age of two years.

In recent years she has only suffered from about 2 convulsions per year. Her intelligence quotient is 30 (Stanford Revision).

The skin shows a marked ichthyosis on the arms, shoulders, back, buttocks, thighs and legs. On these positions it is very scaly, and elsewhere there is marked xeroderma.

When I examined her the nurse in charge informed me that the patient had been treated in recent weeks with a cod liver oil concentrate ointment. This had produced some slight lessening of the scaliness.

Slight axillary sweating is present, and the breasts and pubic and axillary hair are fairly well developed. Menstruation is normal and regular.

Review of the Literature on the Syndrome of Rud

The association of mental deficiency, epilepsy, ichthyosis and infantilism was first recorded by Einar Rud in 1927.

The patient, a man of 22, also showed anaemia of pernicious type, tetany and polyneuritis. Rud's second case (1929) was in a female of 29 who showed ichthyosis, hypogenitalism, partial gigantism of the long bones and hyperglycaemia of diabetic type.

Two further cases were described by Van Bogaert (1935). The first was a boy aged 16 who suffered from ichthyosis, oligophrenia, epilepsy, infantilism and absence of the secondary sex characters. The basal metabolic rate was -23 per cent, but administration of thyroid produced no improvement, and the seizures were poorly controlled. None of the siblings showed this syndrome, but one sister was epileptic and another was obese and slightly backward.

Van Bogaert's second case, aged 26, had shown ichthyosis from the age of 2 months. This reached its full extent at 7 years, at which age epilepsy commenced. Mental deficiency was marked, and pubic hair was absent. In neither case was any neurological abnormality found.

Stewart (1939) made neurohistological studies in another patient who died from an intercurrent infection. This case showed ichthyosis, idiocy, infantilism, epilepsy, arachnoidactyly and retinitis pigmentosa. Some improvement in the physical state was noted by Stewart following the exhibition of thyroid, but after death the thyroid gland was found to be histologically normal. The changes found in the nervous system were essentially those associated with profound mental defect.

It is likely that the association of these factors is not purely fortuitous, and possibly many cases of the syndrome are, as yet, unrecognised. Present classification of such conditions is only tentative, but it would seem likely that the main features to look for are the presence of ichthyosis, mental deficiency and epilepsy. Infantilism may also be present, but was absent in my cases just described, although case no. 1 showed some deficiency in the secondary sex characters, as did Van Bogaert's second patient.

In his classical review of ectodermal dystrophy with neurological disease, Van Bogaert (1935) groups Rud's syndrome with two other rare conditions - xerodermic idiocy and palmo-plantar keratosis with precocious arteriosclerosis of the nervous system.

The condition of xerodermic idiocy shows interesting similarities to Rud's syndrome. Three cases were described by de Sanctis and Cacchione (1932). In the first few months of life a typical pigmented xeroderma appeared, and was associated with oligophrenia, speech defect, testicular hypoplasia and retarded bodily development. No epilepsy was reported in these cases.

When reporting his case of Rud's syndrome, Stewart (1939) pointed out that his patient's skin condition was nearer that of a xeroderma than an ichthyosis with large fish-like scales. However, he decided to classify his case as one of Rud's syndrome mainly on the grounds that epilepsy was present. Indeed, it is plain that the dry scaliness of his patient's skin was different from the pigmented xeroderma reported by de Sanctis and Cacchione.

Tredgold (1947) in his Text Book, says that the cases reported seem to be sufficiently distinctive to constitute a definite syndrome. Possibly it is related to the syndrome of xerodermic idiocy already mentioned. He provisionally includes the syndrome as a variety of primary amentia, but points out that it may eventually prove to be secondary.

The 5 cases of the syndrome described in the literature, and my own 5 cases, are conveniently summarised in Table No. III.

TABLE No. III

Author	Sex	Age	Ichthyosis	Oligophrenia	Epilepsy	Infantilism	Absence of secondary sex characteristics	Remarks
Rud	M.	22	+	+	+	+		Polyneuritis and anaemia
Rud	F.	29	+	+	+	+		Partial gigantism of long bones. Hyperglycaemia.
Van Bogaert	M.	16	+	+	+	+	+	B.M.R. -23%
Van Bogaert	M.	26	+	+	+		+	
Stewart	M.	21	+(Xeroderma)	+	+	+	+	Arachnoidactyly. Retinitis pigmentosa.
Ewing: No. 1	M.	19	+	+	+		+	
No. 2	F.	20	+	+	+			Small stature
No. 3	F.	62	+	+	+			Talipes equinovarus
No. 4	F.	51	+(Xeroderma)	+	+			
No. 5	F.	39	+	+	+			

Table summarising all reported cases of Rud's syndrome including 5 cases described in the present paper.

From the foregoing table it is seen that the really consistent features are the associated ichthyosis, oligophrenia and epilepsy. I wish therefore to suggest that the concept of the syndrome of Rud should be altered to include cases showing these features alone, and that the presence of infantilism should not be considered to be essential. Such a syndrome is probably not uncommon, although only a total of 10 cases can be tabulated to date. My own case no. 1 was encountered in the course of psychiatric practice; the other 4 cases were found in a population of 673 mental defectives (Groups 1 and 2).

It seems likely that increasing knowledge of the association of congenital skin disorders with mental deficiency will lead to new examples of this syndrome being reported, and new syndromes may be discovered.

At the present time it is impossible to state the significance, if any, of such an association of ichthyosis, epilepsy and mental deficiency. However, it is undoubted that the classification of the mental deficiencies is as yet incomplete, and classification is the first step towards a scientific method of studying any such problem.

Some of the possible implications from the existence of such syndromes are included in the general discussion.

DISCUSSION

Introduction

It is now necessary to consider the interpretation of the clinical findings which have been reported, together with the relevant literature, some of which has already been surveyed.

The basic fact which has been demonstrated is that the dyskeratoses have a significant relationship with the oligophrenias, particularly mongolism and those oligophrenias which seem to be of primary type. A statistical study of this nature does not show why there is a relationship between these two conditions. While it is claimed that this survey of the skins of mental defectives and control subjects is the only valid comparison reported up to the present time, it is clear that many uncontrolled factors enter in. For example, it was not possible for me to examine patients without knowing which were oligophrenic and which were not. Certainly this might lead to the tendency to classify a doubtful case in a mental defective as a "dyskeratosis" and a similar condition in a non-mental defective as "normal". While a conscious effort was made to eliminate such bias, it is well known that unconscious tendencies cannot entirely be disregarded, and that rigid controls should be applied whenever possible.

It is therefore hoped that the present paper will stimulate a more fully controlled approach to the problem on the part of experimenters. For example, a group of workers might arrange to present patients to a dermatologist for diagnosis, keeping the head of each patient out of view, and thus eliminating any tendency for the dermatologist to diagnose the presence or absence of oligophrenia from the facial appearance.

Many other variable factors cannot be accounted for in the statistical surveys that have been conducted. For example, many unknown environmental quantities and qualities enter the picture in such matters as diet, care of the skin, more or less exposure to the weather, and so on. Similarly it cannot be said that the foregoing clinical studies prove that oligophrenia itself is related without doubt to the dyskeratoses. It might be, for instance, that oligophrenics are more liable to show dyskeratoses because of some inherent defect which is itself linked with the oligophrenia. For example if liver disease is more frequent in oligophrenia it might itself lead to a metabolic disturbance of vitamin A with associated skin abnormalities. Such a possibility would accord quite well with Benda's findings of liver disease in mongolism and with my findings of the highest dyskeratoses rate in mongoloids. Further research is necessary before any final conclusions can be drawn, but in the following discussion I will tentatively suggest theories which fit the facts as known at present.

Before considering such theories it is pertinent to refer to the question of diet. In my second clinical study I compared mental defectives with chronic psychiatric patients who have been receiving exactly the same diet for years. The significantly higher incidence of the dyskeratoses in these mental defectives does suggest that dietary factors alone cannot account for the skin disorder. The only possible dietetic explanation would be that a higher percentage of the mental defectives fail to eat enough of the available diet. However, I did not find evidence that this was so.

The facts do suggest that in the mental defectives there is a higher incidence of some metabolic disturbance or of some failure of epithelial tissue (possibly damaged by genetic or other factors) to utilise available vitamin A. Another possibility is that the dyskeratoses are entirely genetically induced and are not related to vitamin A metabolism. However, in considering possible explanations for my clinical findings the question of the rôle of vitamin A had to be explored, and this has led to some interesting speculations which will be reported in the following discussion.

As will be shown in the following pages the possible significant relationship between oligophrenia and dyskeratoses may be used as a new approach to the aetiology of mental deficiency. Such a discussion will lead me to suggest several new avenues for investigation of mental deficiency, all of which will fill in the gaps in our knowledge, and some of which may lead to clues concerning the prevention of at least some varieties of oligophrenia.

Quite apart from such useful results which may appear in following the leads suggested in the present studies, my findings do confirm the impressions of others. For example, Touraine (1947) has proposed the use of the term "oligophrenic ectodermoses", and Gibson (1950) has pointed out the need to recognise the "cutaneous" group of mental defectives. The present paper reinforces this need, and suggests that a wider classification of oligophrenias is required.

The hereditary nature of these skin disorders has been postulated for many years. It has also been known that the condition may not manifest itself until after several years of life. For instance, Hardaway

(1898) noted that ichthyosis is not well developed until some months or years after birth, and increases in severity up to the time of puberty. He quotes Boeck as finding Darier's disease making its appearance between the ages of 8 and 16. Many more recent writers on the subject record similar opinions, and Becker and Obermayer (1941) state that Darier's disease on rare occasions may appear as late as the seventh decade. In my clinical survey of mental defectives, it was noticed that the frequency of dyskeratoses in adults (14.5%) significantly exceeded that in children (2.0%).

It is well known that the pathological effect of an unfavourable gene can appear at any time during life. Probably the best known example of this in psychiatry is Huntington's chorea, in which symptoms usually appear in early middle life. In the dyskeratoses, therefore, we may be dealing with a condition in which the expression of the unfavourable gene is merely variable in the time of its appearance.

On the other hand it is possible that the skin changes are themselves a manifestation of some other disorder. This might be, for instance, an endocrine or metabolic disturbance or some other factor which is as yet unsuspected.

For the purpose of simplification the discussion will now consider some of the known facts and possible theories for the significant relationship of dyskeratoses and oligophrenia under the following headings: -

- Metabolic
- Endocrine
- Genetic-developmental
- Psychosomatic

I METABOLIC

On earlier pages I have already presented some of the conflicting evidence on the subject and concluded that at present the aetiology of the dyskeratoses is unknown, although nutritional factors may be involved. However, we are faced with several definite claims of therapeutic success with vitamin A, as well as with the conclusion of Peck, Glick, Sobotka and Chargin (1943) that there is a hereditary or acquired weakness in absorption of provitamin A.

It will be recalled that Frazier et al. (1936 and 1943) found progressive skin manifestations of vitamin A deficiency with increasing age. A simple xerosis was the earliest sign, and keratosis follicularis developed particularly towards puberty. They concluded that the full follicular eruption characteristic of vitamin A deficiency occurs only with attainment of sexual maturity. On the other hand, if there is a clear association between such skin changes and puberty, it is surprising that other clinicians have not drawn attention to it. It is certain, however, that most cases recorded have appeared in the first and second decades, so such a relationship may indeed exist. One possibility is that only certain instances of keratosis follicularis are associated with vitamin A deficiency, and that other examples have some other cause.

If we assume for the moment that vitamin A deficiency does indeed produce some examples of keratosis follicularis, we are faced with the question of what causes the deficiency. Here, we have Leitner's and Moore's (1948) findings of impaired liver function in five out of six cases. Possibly Porter's and Brunauer's (1949) failure to confirm this, and the fact that four out of five of their cases had normal levels of plasma vitamin A, was because their cases had skin changes of a different aetiology.

The importance of the liver in vitamin A metabolism may be conveniently summarised here. Firstly, it appears that carotene (a precursor of vitamin A) is not absorbed in the absence of bile salts (McLester, 1949). Secondly, the conversion of carotenoids into vitamin A is believed to take place in the liver (Jensen and With, 1939) although Sexton et al. (1946) have considered evidence pointing to the intestinal wall as the possible site for conversion. Thirdly, it appears that the liver stores 95 per cent of the body reserves of vitamin A, and that stores are markedly low in disease of the liver, notably cirrhosis (Ralli et al., 1941).

In a later study Porter (1951) examined the plasma vitamin A levels in patients with dyskeratoses. In groups of patients with keratosis palmaris et plantaris, ichthyosis, and pachyonychia this level was below the accepted average figures. Administration of vitamin A only occasionally produced improvement (for example in one case out of nine with ichthyosis) although the plasma levels could be raised to within normal limits. Porter concluded that a metabolic defect was present in these patients. He suggested, for example, that there may be a hereditary defect in the development of epithelial cells so that they cannot fulfil their varying functions, one of which is the metabolism of vitamin A.

In experimental vitamin A deficiency in rats, Wilson and Warkany (1949 and 1950) found developmental anomalies in the offspring. Warkany (1947) points out that if deficiencies of specific nutrients (such as vitamin A) occur during pregnancy in experimental animals, the tendency

towards a congenital malformation may become more frequent. Leitner (1951) states that it is unjustified to apply the results of such experiments to man without reservation. However, he believes it is plain that the development of organs may be similarly altered by either genetic or environmental factors.

Mellanby (1939) studied the effects of vitamin A deficiency on young dogs. He found that bony overgrowth of the skull resulted in compression of nerves. Sometimes the pituitary body was compressed between the overgrown anterior and posterior clinoid processes. Elongation and degeneration of cells in parts of the anterior lobe of the pituitary were sometimes seen.

Mellanby (1941) also describes such overgrowths as producing degenerative changes in the brain and in cranial and peripheral nerves.

Similar studies of avitaminosis A in young rats have led Wolbach and Bessey (1942) to report some important conclusions. These concern (1) epithelial tissue, (2) the teeth and (3) bone and the nervous system. They will be summarised here: -

(1) Epithelial Tissue: Avitaminosis A first leads to an atrophy of the epithelium concerned, followed by a reparative proliferation of basal cells with growth and differentiation of the new products into a stratified keratinising epithelium. This description applies to tissues such as the skin where the epithelial cells arise from a basal germinal layer, whereas in epithelial tissues such as that of the liver (where there is no basal layer) only atrophy without keratinisation occurs.

(2) Teeth: Avitaminosis A leads to atrophy of the enamel organ, then atrophy and failure of polar deposition of dentin matrix on the part of the odontoblasts.

(3) Bone and Nervous System: Avitaminosis A leads to retardation of endochondral bone formation. If the deficiency is established at a sufficiently early age, skeletal growth becomes retarded in a unique manner a considerable period before the rate of increase in weight is materially affected. The C. N. S. and other soft tissues continue to grow at approximately their normal rate until general inanition effects appear, as shown by stationary weight or loss of weight. The result of this is an overcrowding of the cranial cavity with distortion of the brain. Similarly the spinal cord may be compressed and show herniations of nerve roots into intervertebral foramina and into the bodies of the vertebrae. Wolbach and Bessey thus found a mechanical damage of the C. N. S. with irregular degeneration of nerve roots, peripheral nerves and of nerve fibres in various tracts of the spinal cord and brain. They believe that the neurological lesions of vitamin A deficiency are wholly mechanical in origin. They were unable to find premises corresponding to Mellanby's in regard to osteo-blastic and osteo-clastic activities, and did not understand his statement in explanation of bone overgrowth.

Previously, Irving and Richards (1940) had shown that rats suffering from vitamin A deficiency from the time of weaning develop degeneration of the medullary funiculus praedorsalis so consistently that this change can be used in the biological assay of vitamin A.

Now we can consider these experimental animal studies in relationship to man, and in particular to oligophrenia. In considering the developmental anomalies produced in vitamin A deficient rats' offspring by Wilson and Warkany (1949 and 1950), Mautner (1951) showed that these

anomalies were analagous to the condition of ostium atrioventriculare commune, which has only been demonstrated in mental defectives suffering from mongolism.

This may be an important relationship in view of my finding that the highest percentage occurrence of dyskeratoses (50.0%) was in the mongoloid group.

Benda (1949) has expressed the view, which is supported by his experimental studies, that mongolism is a condition of "pituitary cretinism". He believes that the mongol neonate is suffering from the results of deceleration of the developmental rate, due to noxious agents interfering with the proper blood supply and nutrition of the growing foetus. Thus, the mongol is born with a hypopituitarism which prevents normal growth after birth. The skull, although within normal limits at birth, shows a remarkable retardation during the following years, and moreover the foetal proportions (relatively small face) are retained. The delay in growth of the skull is in the length of the base, and Benda has no doubt that the outline of the frontal lobes, the distortion of the temporal lobes and the compression of the occipital lobes of the brain are the result of the impact of the pathological skull.

This description, of mechanical damage to the brain in mongolism, strikes one as remarkably similar to that described by Wolbach and Bessey in young rats deprived of vitamin A.

In the case of the liver in mongolism Benda finds fatty vacuolisation, fibrosis, degeneration of the parenchyma and congestion with some regularity. Out of a group of thirty-one mongoloids over two years of age, only one had a normal liver - and that was a borderline case of mongolism.

In this respect we might again wonder if impaired vitamin A metabolism could be a factor in producing such pathological changes.

Benda's studies have led him to reject the genetic theory for mongolism and to conclude that environmental factors in utero are operative. With regard to the skin changes he concludes that the fine skin of the mongoloid neonate becomes dry, thick and rough in proportion to the degree of thyroid deficiency present.

It is a well-known fact that mongoloids are very susceptible to develop intercurrent illnesses such as respiratory diseases. It has also been recognised both clinically and experimentally that avitaminosis A leads to keratinising changes of all epithelial tissues (Wolbach and Bessey, 1942). Blackfan and Wolbach (1933) found a high mortality rate in infants with respiratory disease who suffered from avitaminosis A. Indeed vitamin A has been called the "anti-infective vitamin" because of its function in maintaining epithelial integrity. This again leads to the thought that susceptibility to infection in mongolism may be a reflection of impaired vitamin A metabolism.

Leitner (1951) draws an analogy between induction of congenital anomalies by maternal rubella and deficiency of specific nutrients during pregnancy producing the same effect. He has shown in previous work that plasma vitamin A levels fall in infections and fevers, and goes on to suggest administration of large doses of the vitamin to pregnant women with infection or fever, in the hope of preventing congenital defects in the child. Bicknell (1950) was the first to suggest that maternal rubella may produce mental deficiency in this way. He advises that the vitamin be given by injection of an aqueous dispersion,

as oral administration fails to raise the plasma level during fever.

It seems equally possible that such a fall in the maternal vitamin A level could occur due to non-specific fever or metabolic changes. Whether such a factor could be incriminated as causing mongolism or any other variety of oligophrenia remains to be seen. However, we have already considered some comparisons which tend to turn our attention to the possibility of vitamin A being implicated in some way in oligophrenia. These points might be tabulated here: -

- (1) The higher incidence of dyskeratoses in oligophrenia (particularly mongolism) and the belief of some clinicians and experimenters that the dyskeratoses represent a disturbance of vitamin A metabolism.
- (2) Mautner's (1951) analogy between the heart malformations in mongolism and those in rats born of vitamin A deficient mothers.
- (3) The skull changes found in mongolism (Benda) and their similarity to those in young vitamin A-deficient rats (Wolbach and Bessey).
- (4) The high incidence of pathological changes in the livers of mongoloids, and the fact that avitaminosis A produces liver disease in experimental animals.
- (5) The high incidence of respiratory infections in mongoloids, and the fact that avitaminosis A is known to increase susceptibility to such infections.
- (6) As a final point I will mention a subject which will be discussed in the next section (Endocrine). However it is pertinent to notice now that some comparison may be drawn between the pituitary and gonadal changes found by Benda in mongolism, and the results of avitaminosis A on these glands in experimental animals.

While it is true that any attempt to relate the above facts is purely speculative, I feel justified in so doing on the grounds that any theoretical conclusions may be later tested by experiment.

We may postulate that under certain conditions of pregnancy, vitamin A requirements of the foetus may not be fulfilled. By analogy with experimental animals it would seem possible that this might lead to developmental abnormalities such as mongolism and possibly other types of oligophrenia. It is plain that such a deficiency could not directly influence the development of a dyskeratosis some years after birth. However two possibilities can be considered in this respect. One is that an avitaminosis A might produce organic damage in the foetus which is expressed as oligophrenia and as a metabolic disorder such as may be present in patients suffering from dyskeratosis. The second is that some inherent disorder in the foetus prevents proper utilisation of available vitamin A.

These two possibilities will now be considered in a little more detail: -

(1) As already stated, various workers have postulated metabolic or liver disease as the primary cause of an inability to handle vitamin A, with resulting dyskeratosis. Leitner (1946) suggests that dyskeratosis follicularis may be an end result of a disease of metabolism where various other factors have first produced a liver disturbance. We have seen Wolbach's and Bessey's (1942) experimental findings of liver damage being produced by avitaminosis A. Could it be possible then, that such an avitaminosis might induce liver damage during the foetal stage, which is later evidenced by a dyskeratosis? If so, the skin changes in mongolism would be secondary to the liver damage described by Benda, and not to the hypothyroidism as he postulated.

If exposing the foetus to an avitaminosis A might produce an oligophrenia (with dyskeratosis in later life) we still have to consider my findings of a higher dyskeratosis rate in mongolism. In this disease there are many known instances of twins in which one was a mongol and the other was normal (Benda, 1949; Morris and MacGillivray, 1953). This creates a stumbling block in accepting the above theory, which otherwise utilises the inadequate number of facts that are available. It is just possible, however, that a maternal deficiency of vitamin A might have a more adverse effect on one twin if, for instance, that twin had already a poorer access to the placental circulation by virtue of its position. Benda does believe that noxious factors during pregnancy might affect only one of twins by such a mechanism.

(2) The other possible explanation, which might fit the facts at present under consideration, is not that a maternal avitaminosis A produces foetal damage, but that some inherent disorder in the foetus prevents it from properly utilising the vitamin A available to it from the placental circulation. Under these circumstances the foetal development might be hindered, and if the abnormality continued after birth it might be reflected by development of dyskeratoses. The cause for such an abnormality in vitamin A metabolism might be genetic, and of course there are still some workers (Tredgold, 1947; Penrose, 1951) who support the genetic theory of mongolism. A report of Chen, Tsai and Kuo (1944) throws some light on this subject. They examined a girl of 25 who had a congenital hypotrichosis and dystrophy of nails. She was malnourished and was found to show practically all the known characteristic ectodermal manifestations of avitaminosis. These protean manifestations were never noticed in

other similarly malnourished subjects, some of whom were on the same institutional diet as the patient. This fact led these workers to suggest that the congenitally deficient tissue is low in vitality and has a lower threshold to the effects of avitaminosis.

It would be difficult, however, to reconcile a genetic theory with the statement of Benda (1949) that mongolism can occur in one of monozygotic twins.

We do have evidence of constitutional differences between individuals in their metabolism of vitamin A. Lund and Kimble (1943) studied vitamin A levels in pregnancy. They noted wide variations in plasma values of vitamin A in newborn twins. Barnes (1951) studied the placental metabolism of vitamin A because of the reports tending to indicate that foetal deficiencies may be responsible for congenital abnormalities. His main conclusion was that the principal transfer to the foetus takes place in the form of carotene, and that the foetal system converts the carotene to vitamin A and stores it in high concentration in the liver. He therefore believes that intra-uterine vitamin deficiencies would seem to result either from long-standing maternal deficiency of carotene, or from a failure in the regulating mechanism which controls foetal conversion of carotene to vitamin A.

Porter (1951) points out that vitamin A deficiency is endemic in China, yet there is no evidence that more children are born there with abnormal skins. The same could be said for the incidence of mongolism, thus tending to ascribe the metabolic disorder to some inherent defect in the foetus, if indeed vitamin A is an aetiological factor. (Another possible explanation for this will be discussed in the section on Genetic-developmental factors.)

The above theories are propounded purely tentatively. They do embrace some of the experimental and clinical facts that are known at present, and the first theory would seem to be the more satisfactory one. Future developments will show whether or not vitamin A metabolism is concerned with the occurrence of oligophrenias, and in particular, of mongolism.

My own findings (of higher incidence of dyskeratoses in mongolism) may merely be a reflection of a degree of liver damage not present in oligophrenia in general, and liver changes themselves may be due to some endocrine or other factor. In a similar way Mautner's findings concerning the cardiac abnormalities may not be significant, and this may also be true of the rats' skull changes found by Wolbach and Bessey. However, it is not too early to develop theories which fit our present knowledge, and to test the theories by future findings and experiments. For instance, as stated already, it seems desirable to institute large-scale controlled experiments on the use of vitamin A in human pregnancy. Bicknell (1950) suggested its use in rubella, and Leitner (1951) its use in all fevers and infections of pregnancy. It might be desirable to administer the vitamin to a group of pregnant women irrespective of clinical evidence of infection, as latent infections may be important. As the incidence of mental defective births is low, a large number of mothers would have to be used. An initial smaller scale experiment might utilise pregnant women near the menopausal age, as they are known to have the highest incidence of mongol births.

Of course, metabolic studies of patients with mongolism and of their mothers are indicated.

Before leaving the subject of vitamin A administration in pregnancy, attention should be drawn to the findings of Cohan (1953) who administered excess of vitamin A to pregnant rats. He found a reduction of the number of litters carried to term (10% as opposed to 38% in control group). There was also an incidence of 50% of gross anomalies of development of the skull and the brain in these offspring, whereas no such anomalies appeared in the control group. This would suggest that there is an optimal range of vitamin A dosage, as there is for other dietary essentials. Excessive administration of vitamin A to pregnant mothers might lead to distressing anomalies in the human infant as in the rat.

The findings of Barnes (1951) already reported, suggest that carotene may be the substance of choice to be administered.

II ENDOCRINE

We will now consider some of the known associations between endocrines, dyskeratoses and oligophrenia, first dealing with certain individual endocrine glands.

(a) Thyroid: The relationship of the thyroid secretion to dyskeratoses is still not clear. We have already considered the report of Helman (1947) of cases of sporadic cretinism and ichthyosis in the same family. The generally poor response of ichthyosis to thyroid therapy has been mentioned as have the researches of Porter (1926). There is no doubt that the conditions of ichthyosis and keratosis follicularis are different to the puffy, dry, thickened skin as seen in hypothyroidism, either congenital or acquired. Probably they are changes of the latter kind that Benda (1949) finds proportionate to the degree of thyroid deficiency, and he does not specifically mention the dyskeratoses.

In reviewing the literature on thyroid dysfunction one has again to consider vitamin A. Wilder et al. (1940) report that thyroid is essential for the conversion of carotene into vitamin A and also for the storage of vitamin A. Eddy and Dalldorf (1944) state that there are some reasons to believe that the formation of vitamin A is dependent on thyroid function. Thus, removal of the thyroid gland of goats causes the milk to become pigmented with carotene, and these authors have noted metaplastic changes in the thyroid glands of rats deficient in vitamin A. It is not yet clear if such a relationship occurs in the human, but here too is a matter deserving investigation. The same authors report that cases of exophthalmic goitre were shown to have abnormally small amounts of vitamin A in the blood plasma, and this returned to normal after thyroidectomy.

Possibly any thyroid disturbance in avitaminosis A is secondary to pituitary changes such as are about to be described.

(b) Pituitary: Laubenthal's (1940) conclusions have already been referred to. He postulated that ichthyosis and associated diseases have a common functional basis with the point of attack in the diencephalic-hypophyseal system. In this respect we might recall some of the skeletal and other abnormalities that have been reported in cases of Rud's syndrome:- Partial gigantism occurred in one of Rud's cases and is possibly a reflection of pituitary eosinophilic cell disorder. The hyperglycaemia which was also present might similarly have been caused by anterior pituitary overactivity. Other abnormalities which are probably of pituitary origin are hypogonadism and dwarfism, and it will be recalled that Cockayne regards small stature as part of the fully developed and severest form of Darier's disease. In reviewing xeroderma pigmentosa, Elsasser et al. (1950) considered that one seventh of all cases showed evidence of associated infantilism or dwarfism. A recent case of Joulia, Texier and Fruchard (1952) also showed marked pituitary dysfunction, and Sonneck (1952) has commented on the association of ichthyosis with cryptorchidism.

We have already considered Goodman's (1938) report of therapeutic success using extract of whole pituitary glands to treat keratinised pilosebaceous apertures. He was led to wonder if there was a relationship between the pituitary hormones and vitamin A. This is, indeed, described by Sutton and Brief (1938) who examined vitamin A-deficient male and female rats. The basophilic cells of the pituitary were found to be increased as they are after gonadectomy. The effect was most pronounced in males, and was thought probably to be attributable to the gonadal

injury caused by the avitaminosis. Eddy and Dalldorf (1944) report that avitaminosis A leads to atrophy of many organs, especially testes, thyroid, pituitary, salivary glands, liver and spleen. They state that in the pituitary glands of cattle an increased number of alpha cells in the anterior lobe has been frequently noted.

Benda's (1949) description of the pituitary changes found in mongolism is not identical, but it is interesting to note that he too believes that one type of change is apparently a symptom of thyroid and gonadal dysfunction, and is associated with colloid stasis in the thyroid and pituitary. This may also be observed in dwarfism, and Benda reports that the only non-mongoloid control cases in which he observed extreme colloid accumulations in the pituitary cleft and tubules, showed similar alterations in the liver as are seen in mongolism. An interesting parallel is to be found in the report of Madsen et al. (1942) that serous cysts form between the anterior and posterior pituitary lobes in young animals depleted of vitamin A.

Benda points out that observations of the pituitary in man and animals after castration are not entirely consistent. He does find, however, that beta cells regress to "castration cells" or delta cells, which may be related to the gonadal hypoplasia.

It may be that the liver dysfunction produces an abnormal metabolism (or reduced absorption) of vitamin A, which leads to gonadal dysfunction followed by pituitary changes. Whether a metabolic disturbance of vitamin A could directly produce alterations in the growth of the skull, or would do so via the endocrine system, would be a matter for future clarification. The significant point to be emphasised now is that, when considering the

rôle of the pituitary in dyskeratoses and in mongolism, we are again led to information which seems to implicate vitamin A metabolism.

Benda has concluded that a pituitary disorder is present in mongolism, and indeed refers to mongolism as a congenital acromicria - the opposite of acromegaly. He postulates some noxious factors during gestation as causing this. However the discussion in the previous section on metabolism did suggest the possible implication of vitamin A.

In the treatment of mongolism Benda (1949) uses thyroid and pituitary extract as have other workers (Bailey, 1947; Cook, 1950). He feels that we require to find some "growth hormone having a beneficial chondrotropic action upon the bone cartilages and having, at the same time, a mild stimulating influence upon the body cells and the other endocrine glands." At present he uses pituitary extracts from immature animals in the belief that these contain more growth hormone. While no one claims a cure of mongolism by such methods, Benda and others do believe that beneficial results occur.

(c) Adrenals: In a case of Thannhauser's (1936) suffering from anhidrotic ectodermal dysplasia there were signs of adrenal medullary insufficiency. The adrenal medulla is of ectodermal origin, and might thus be involved in such a dysplasia. The same patient, however, also showed exostosis of the inner table of the skull which is of mesodermal origin. Apart from this instance there is a paucity of reports of adrenal dysfunction in oligophrenias, except in Benda's book where he describes finding a striking and consistent pathology of adrenals in all mongols over four years of age. Such changes could be secondary to the pituitary hypofunction.

The use of cortisone by Coste et al. (1952) to improve ichthyosis vulgaris has already been mentioned.

(d) Gonads: The lack of well-developed secondary sex characters has long been recognised in mental deficiency, and it is also known that many patients have atrophic gonads. In the examples of Rud's syndrome already described there were four cases with infantilism, and two more with absence of secondary sex characteristics. The literature contains no authenticated reports of procreation by mongoloids, and hypoplastic gonads are found by Benda.

The fact that avitaminosis A leads to gonadal atrophy has already been reported.

General discussion on endocrines: The above illustrations serve to show that endocrine disturbances are not uncommon in oligophrenics and sufferers from dyskeratoses. At present we only have a few isolated facts, to which new material will certainly be added in the future. The nature and aetiology of these disorders remain to be shown. In some cases a genetic factor may be responsible, but certainly the possibility of noxious factors during gestation deserves to be explored. At least in the case of the thyroid, pituitary and sex glands we have considered evidence that vitamin A is implicated in some way. Further experimental and clinical work in this region is indicated, and we might hope to know some day whether or not these endocrine disturbances are actually due to some metabolic disorder.

It certainly is tempting to speculate on the possible relationship between vitamin A and the "growth hormone", the need for which is expressed by Benda. Certainly in the present consideration of the problem we are

constantly brought back to the subject of vitamin A. In addition we have reviewed reports of the importance of vitamin A for endochondral bone formation, and for normal functioning of the liver, pituitary, thyroid, gonads, etc. As far as our present knowledge goes, therefore, we may say that vitamin A may possess some of the properties defined by Benda as necessary in his "growth hormone."

III GENETIC-DEVELOPMENTAL

Now we shall consider the possibility that genetic factors alone account for the occurrence of the so-called primary oligophrenias, and the dyskeratoses (whether these conditions appear alone or in association).

The geneticists have been quoted in the earlier part of this paper, giving their views on the inheritance of ichthyosis, Darier's disease, etc. Their attempts to describe inheritance patterns for such disorders have been much more successful than in the oligophrenias. Even so, by no means all instances of dyskeratoses can be thus accounted for, and the genetic explanation then given is that such cases have arisen de novo, by mutation. As was pointed out at the beginning of this discussion the dyskeratoses could be secondary to some metabolic or other disturbance which is itself genetically determined. In the section on metabolism we considered one possible theory - that a genetic disturbance giving rise to improper utilisation of vitamin A could thus lead to development of dyskeratoses, and might be a factor in producing mental deficiency. A genetic predisposition to develop some abnormality may not always show itself without some other precipitating factor. Evidence of this is recapitulated by Leitner (1951), including the findings by Warkany (1947) of the significance of adequate vitamin A supplies for normal development of the foetus. Leitner shows that it appears that a latent tendency to a congenital trait (which may only rarely become manifest under adequate nutritional conditions) may become more frequently overt if the diet during pregnancy lacks certain nutrients.

In the discussion on metabolism we have already considered another theory which fits the facts known at present, involving the idea that a noxious factor (such as avitaminosis A during gestation) leads to abnormalities of brain development, and liver damage with subsequent dyskeratosis. However, this would not explain why only some cases of mongolism

show obvious dyskeratoses. This could be accounted for by postulating that in some cases a genetic tendency towards development of dyskeratoses only manifests itself when enhanced by avitaminosis A or other nutritional defect during gestation. Thus, if some such noxious factor does operate during the gestation of oligophrenics, and if there is a genetic factor tending to produce dyskeratoses, we might find the dyskeratoses only in mongoloids who had that genetic tendency. It appears possible that a noxious factor may affect only one of twins, possibly depending on the relative foetal access to the placental circulation. Here, then, is a possible mechanism whereby mongolism and an enhanced tendency towards dyskeratosis might appear in only one twin, even if these twins were monozygotic.

Penrose (1951) has analysed all available data on familial mongolism in which degree of relationship and maternal age are specified. He suggests that mongolism could be due to a very common gene (frequency 1 in 5 in the general population) and that all homozygous fetuses are susceptible. They have a frequency of 1 in 25, but only about one case in 27 is actually affected, leading to an absolute incidence of 1 in 675 at birth. Manifestation of the condition is, he feels, largely controlled by factors concerned with maternal age. Maternal age is significantly lowered in cases showing inheritance through the mother. To account for this, Penrose suggests that the defensive effect of young maternal age over the susceptible foetus is reduced when the mother herself is a mongoloid or a potential mongoloid. Penrose makes no suggestions about the pathology of the process by which maternal age exerts its peculiar aetiological influence.

Many workers have suggested that maternal age influences the foetus in various ways, including over-age of the ovum (Geyer, 1939), endometrial disorders (Engler, 1949) and endocrine disturbances (Benda, 1949).

It has recently been suggested that serum vitamin A levels may influence fertility. Laurence and Sobel (1953) report that serum vitamin A fluctuations appear associated with the menstrual cycle, and thus may be hormonally influenced. Serum concentrations were maximal at the 14th. and 25th. days of normal menstrual cycles, and such changes did not occur in two patients with abnormal cycles. These workers conclude that an upset in the cyclic rise and fall of the serum vitamin A levels may have some bearing on certain types of infertility in which ova are not produced, or in which fertilised ova do not become securely implanted in the uterine wall.

This report leads us to speculate as to what would follow if a pregnancy actually did follow such insecure implantation of a fertilised ovum. Might this lead to foetal maldevelopment, and be similar to the endometrial disorder postulated by Engler (1949) as the cause of mongolism?

The present paper has drawn attention to the question of vitamin A metabolism, and it is possible that increasing maternal age might make metabolic disorders more likely.

If such a disorder were to produce insecure implantation of the ovum (and we have seen that it might also enhance the appearance of a latent genetic tendency) it would not necessarily always be the immediate cause. For example, it would not be necessary to postulate this occurrence in the case of a mongoloid born of a homozygous mother, as suggested by Penrose. Therefore, if Penrose is correct, and if an avitaminosis A during gestation is associated with dyskeratoses, we might expect to find a lower incidence of dyskeratoses in mongoloids born of young mothers, and a higher one in those born of older mothers. A study of this question should be quite possible, and I have attempted to investigate it on a small scale. In

TABLE No. IVMongoloids with dyskeratoses.

Mother's age $X_1 - M_1$ $(X_1 - M_1)^2$
at patient's
birth

38	-0.67	0.4489
41	2.33	5.4289
44	5.33	28.4089
40	1.33	1.7689
42	3.33	11.0889
34	-4.67	21.8089
42	3.33	11.0889
32	-6.67	44.4889
40	1.33	1.7689
34	-4.67	21.8089
46	7.33	53.7289
31	-7.67	58.8289
<u>464</u>		<u>260.66</u>

Mongoloids without dyskeratoses.

Mother's age $X_2 - M_2$ $(X_2 - M_2)^2$
at patient's
birth

27	-8.5	72.25
41	5.5	30.25
24	-11.5	132.25
43	7.5	56.25
45	9.5	90.25
40	4.5	20.25
25	-10.5	110.25
36	0.5	0.25
40	4.5	20.25
34	-1.5	2.25
<u>355</u>		<u>534.5</u>

Mean maternal age (M_1)=38.67years. Mean maternal age (M_2)=35.5years.

$$\begin{aligned} \text{S.D. (Of pooled groups)} &= \sqrt{\frac{(X_1 - M_1)^2 + (X_2 - M_2)^2}{(N_1 - 1) + (N_2 - 1)}} \\ &= \sqrt{\frac{260.66 + 534.5}{11 + 9}} = \underline{6.265} \end{aligned}$$

$$\text{S.E.}_D = \text{S.D.} \sqrt{\frac{N_1 + N_2}{N_1 N_2}} = 6.265 \sqrt{\frac{22}{120}} = \underline{2.6820}$$

$$\text{C.R.} = \frac{D}{\text{S.E.}_D} = \frac{3.17}{2.682} = \underline{1.181}$$

From a table of t and with 20 degrees of freedom the above Critical Ratio of 1.181 shows the probability (P) to lie between 0.50 and 0.10.

Thus, there is no statistically significant difference between the mean maternal ages in the above two groups.

Table showing the maternal age at the time of birth in the cases of 12 mongoloid patients with dyskeratoses and 10 mongoloid patients without dyskeratoses. A statistical test for the reliability of the difference between the two mean maternal ages is also shown.

the case of the 22 North Carolina defectives with mongolism, I studied the files for information concerning the mother's age at the time of the patient's birth. This was available (by calculation) from a questionnaire in which the mother stated her age at the time she made application for the child's admission to hospital. I feel, however, that we cannot place too much reliance on these figures which depend entirely upon the veracity of the mother. For instance, one mother gave her present age as 40 years. In the same file a letter from the father dated 10 years later stated that the mother had just died at the age of 59. (In all instances such as this I took the greater age to be the more correct one.)

These maternal ages are shown in Table No. IV. These figures have been examined statistically using the formulae given by Garrett (1947) for the reliability of the difference between means in small independent samples. Table IV shows that there is no statistically significant difference, although the mean age of mothers of mongoloids without dyskeratoses is 3.17 years lower than that of mothers of mongoloids with dyskeratoses. This small number of cases cannot be said to disprove the theory suggested above. It is necessary for this question to be studied in larger groups in which the accuracy of the mothers' ages is beyond doubt.

Penrose's genetic theory might also explain why we do not have reports of a higher incidence of mongolism in countries where avitaminosis A is endemic. His figures are based on cases in Eastern Europe and the United States of America. It has been stated by Thompson (1939) that the incidence of mongolism in Caucasian stock is not applicable to all stock. For instance, the incidence is significantly lower among American negroes. It might therefore be that the common recessive gene postulated by Penrose is not as frequent as 1 in 5 in other (non-Caucasian) stock.

On the other hand, Yannet (1953) states that studies in the Netherlands during the German occupation supply a human experiment of the effects of nutrition during pregnancy although, of course, many other complicating factors exist. The diets of pregnant women are said to have been grossly deficient in vitamin A, and yet the incidence of congenital malformations did not appear to be unusually high. If this is so, it would tend to suggest that, if a defect of vitamin A metabolism is indeed an aetiological factor in such malformations, the defect is an inherent one in the foetus.

To conclude consideration of genetic and developmental factors some opinions of other workers will be briefly reviewed. The common ectodermal origin of the skin and the nervous system has often been referred to. For instance, Halperin and Curtis (1942) concluded that the gene for ectodermal dysplasia has a depressing effect upon the intelligence. Slater (1944) points out that this might be merely a coincidence.

However, my clinical findings described in this paper, and the review of the literature already carried out do suggest that we are dealing with more than a coincidence.

Henrichs (1920) believed that ichthyosis and mental deficiency in his cases were caused by a single gene, though his conclusion was criticised by Cockayne (1933). In finding non-ectodermal structures involved in association with ichthyosis and feeble-mindedness, Laubenthal (1940) was led to conclude that the point of attack was in the diencephalic-hypophyseal system.

None of these reports can be regarded as conclusive concerning the theory that a genetic abnormality affects the primitive ectoderm, and leads to common involvement of the skin and C. N. S.

IV PSYCHOSOMATIC

The rôle of the emotions in diseases is now well recognised and has given rise to the concept of psychosomatic medicine. Emotional factors in dermatology have been clearly described for many years, particularly in the neurodermatoses (Vickers, 1952). Frumess (1953) points out that emotional factors affect two skin diseases of proved organic aetiology - warts and herpes simplex. Williams (1951) found good evidence of maternal rejection in children with atopic dermatitis, and Walsh and Kierland (1947) report similar emotional factors in adult atopic eczema. Psychological factors are described by Wittkower (1946, 1947) in psoriasis and seborrheic dermatitis.

Although in some of these conditions there is a family history of atopy, none of them has been regarded as being genetically determined. However, Mason (1952) announced the fact that a case of ichthyosiform erythroderma was substantially cured by hypnosis. Much correspondence was stimulated by Mason's article (British Medical Journal, Sept.-Oct. 1952) and some wished to question the diagnosis. However there is no doubt that the case described was a well-authenticated example of congenital ichthyosis with abnormal skin present at the time of birth. A histological section was shown to be consistent with changes described in ichthyosis congenita.

The implications of these findings are not yet clear. The literature on hypnosis includes many accounts of the hypnotic production of cutaneous stigmata, blisters, etc. It appears that the entire nervous system, including the autonomic nervous system and the endocrines may be influenced by hypnosis. It may well be, therefore, that the cure of a case of congenital ichthyosis by suggestion involves the hypophyseal-diencephalic system. However, it is interesting to note that Mason cured first one part of the

body and then another, and that the areas being cleared of the disease were strictly under his hypnotic control. This certainly would seem to preclude the possibility that there was any general hormonal effect underlying the cure.

Although there is no clear significance between these findings and the present paper, the demonstration of psychosomatic features in ichthyosis does seem of sufficient importance to warrant its inclusion here.

Conclusions

In three of the preceding sections (those on metabolism, endocrines and genetics), because of various published reports we were inevitably drawn into consideration of vitamin A. This in itself suggests that vitamin A may somehow fit into the pattern of oligophrenias and their association with dyskeratoses. When I first began to search the literature on these subjects I had no preconceived notions on the meaning of such an association. However, the fact that vitamin A metabolism might somewhere fit into the picture kept forcing itself upon me. When I turned to the experimental literature on vitamin A, I found reports concerning its importance in normal growth of the skull, functioning of the endocrines and so on. Some of these studies have not yet been referred to in the literature on mental deficiency, and their possible significance has not previously been commented on.

In the foregoing discussion I have pointed out analogies between such experimental reports and the pathological changes found in oligophrenia, particularly mongolism. This has led me to postulate some theories which may explain the facts as known at present, and which will suggest further experiments.

These theories will now be briefly summed up: -

(1) Avitaminosis A during gestation might produce organic damage in the foetus, which is expressed as an oligophrenia. The simultaneous production of some accompanying metabolic disorder (due, for instance, to liver damage) may then lead to a tendency to develop dyskeratoses. Alternatively, the avitaminosis A during gestation may merely enhance a genetic tendency to produce dyskeratoses. In twins, only one of whom shows, for example,

mongolism, it is possible that a poorer access to the placental circulation had an adverse effect on that twin only.

It is possible that a disturbed maternal vitamin A metabolism (present at the time of conception) may be a factor in preventing normal nidation of the ovum (Laurence and Sobel).

(2) Genetic tendencies towards both dyskeratosis and oligophrenia may be enhanced by avitaminosis A or other nutritional defect. For example, a disturbance of vitamin A metabolism during gestation might lead to the birth of a defective with mongolism and a predisposition to develop dyskeratosis. According to Penrose's theories, young mothers who are homozygous with the foetus (potential mongolism in the mother) would produce mongoloid children without such a precipitating cause during gestation. We might thus expect to find the highest dyskeratosis rate in mongoloids born of elderly mothers. These genetic tendencies might be linked or might exist independently.

(3) An inherent disorder (probably genetic) in the foetus may prevent proper utilisation of vitamin A, leading secondarily to oligophrenia and dyskeratosis. Such a defect might be, for instance, a failure of foetal conversion of carotene to vitamin A (Barnes). It is difficult to accept this theory in view of Benda's statement that mongolism can occur in one of monozygotic twins.

(4) It is possible that both the oligophrenia and dyskeratoses are reflections of the pathological effect of an unfavourable gene which produces a disorder of the primitive ectoderm. The dyskeratoses in this case could be either a direct genetic effect or a reflection of an inability of

ectodermal cells to handle vitamin A metabolism. While this theory is otherwise acceptable, it does not explain, for instance, why there should be a high incidence of dyskeratoses in mongolism and yet some patients escape the skin disorder altogether. However, a closer study of the dietary factors might reveal that the patients showing the dyskeratoses are those who are eating on the average a lower percentage of available vitamin A-containing foods.

A certain degree of therapeutic optimism might be justified if one of these theories could be proved. For example, in the first and second theories we are concerned with an avitaminosis A during gestation, which is presumed to depend upon maternal factors. If this should prove to be an aetiological factor in oligophrenia, it is possible to envisage tests being performed on the mother early in pregnancy and appropriate metabolic treatment being instituted.

In the third theory we presume a defect in the developing foetus which might not be detectable before birth. However, if such a defect were found to be a reality, dietary supplements might prevent at least some growth retardation.

In the fourth theory we presume a genetic, and therefore unalterable, condition. However, we have already considered evidence that metabolic disorders of vitamin A and multiglandular disorders of the endocrine system appear to be associated. If, therefore, an inability of ectodermal cells to handle vitamin A were found to exist, such a disorder might be alleviated by treatment and possibly some secondary glandular defects could thus be improved.

I have evolved these theories as a result of studying the literature in an attempt to explain my findings of a significantly higher rate of dyskeratoses in mental defectives as compared with non-mental defectives. None of the theories can be said to be entirely satisfactory. It is obvious that new findings must be sought and these may indicate the need for still some other explanation. However, the clinical study of the incidence of the dyskeratoses in mental deficiency has at least suggested a new approach to the question of the aetiology of mental deficiency. Some possible further studies will be suggested. At present we simply do not possess enough knowledge to confirm or disprove absolutely any of the theories I have propounded.

SUGGESTED FURTHER STUDY

The conclusions that have been drawn from the present clinical study suggest some new approaches to the study of oligophrenia, and some of these will be listed here:-

Classification: The need is seen for more studies on the classification of mental deficiencies.

In a similar way further studies on the classification and genetics of dermatological conditions may help our understanding of the cutaneous forms of oligophrenias (the oligophrenic ectodermoses of Touraine).

Experimental animal studies: These, it is to be hoped, will help to elucidate the cause of dyskeratoses and developmental defects, also the rôle of vitamin A in preventing such conditions.

Clinical studies of mental defectives: Further studies of the skins of mental defectives are required.

Endocrine and metabolic studies are indicated. The latter would pay particular attention to plasma vitamin A levels, dark dysadaptation, etc.

Trials with vitamin A and carotene are justified in mental defectives of various ages, but particularly in defectives with mongolism as soon after birth as possible.

Clinical studies on mothers of mental defectives: The maternal age at the time of the birth should be compared in mongoloids with and without dyskeratoses. If no significant difference exists here this would tend to suggest that, if vitamin A deficiency is an aetiological factor, the deficiency is due to a disorder in the foetus rather than in the mother.

Endocrine and metabolic studies of the mothers of mental defectives are indicated, again with special reference to vitamin A.

Vitamin A metabolism in pregnancy requires further investigation.

Trials with vitamin A and carotene administration in pregnancy have already been mentioned in the foregoing pages. In particular this is justified in pregnant women nearing the menopause, or who are suffering from infection or fever. However, a large-scale controlled trial, without special reference to these factors, is also desirable.

SUMMARY

1. The literature is reviewed on certain skin diseases in which an association with mental deficiency has been claimed. These include: ichthyosis (vulgaris and congenita), keratosis follicularis (Darier's disease), tylosis palmaris et plantaris, anhidrotic ectodermal dysplasia, xeroderma pigmentosa, and monilethrix.

2. No previous work has been reported in which the skins of mental defectives are statistically compared with those of non-mental defectives. Such a study is now reported comparing (a) a mental defective sample and a general population sample in Great Britain, and (b) a mental defective sample, a general population sample, and a sample of psychiatric patients (receiving the same diet as the mental defectives) in North Carolina, U.S.A.

Only anomalies of keratinisation were found, and they are therefore grouped under the general term of "dyskeratoses."

3. (a) These dyskeratoses are found among mental defectives in a greater incidence which is statistically significant.

(b) Among mental defectives the dyskeratoses are significantly more frequent in adults (over 16 years of age).

(c) A significantly higher incidence of dyskeratoses is found in defectives suffering from mongolism.

(d) The dyskeratoses are found more frequently in association with the types of mental deficiency at present usually classified as primary amentia (endogenous mental deficiency).

4. The syndrome of Rud is discussed, five cases having been described in the literature to date. Five more cases are described.

It is concluded that the cardinal features in this syndrome are ichthyosis, mental deficiency, and epilepsy, and that the presence of infantilism should not be considered to be essential.

5. The significance of these clinical findings is discussed under the headings of metabolic, endocrine, genetic-developmental, and psychosomatic factors.

6. Because of various clinical and experimental findings which are considered, it is concluded that vitamin A metabolism may somehow be implicated in some oligophrenias. Facts pointing to this implication include:-

(a) The higher incidence of dyskeratoses in oligophrenia, and the belief of many workers that the dyskeratoses represent a disturbance of vitamin A metabolism.

(b) Certain analogies between the heart malformations in mongolism and those in rats born of vitamin A-deficient mothers.

(c) The skull changes found in mongolism, and their similarity to those in young vitamin A-deficient rats.

(d) The high incidence of pathological changes in the livers of mongoloids, and the fact that vitamin A deficiency produces such changes in experimental animals.

(e) The high incidence of respiratory infections in mongolism which may be a reflection of disturbed vitamin A metabolism.

(f) Some comparisons between endocrine changes found in mongolism and similar changes produced in animals by avitaminosis A.

7. Possible theories which would account for many of the facts known at present are:-

(a) Avitaminosis A during gestation may lead to organic damage

in the foetus, expressed as oligophrenia and a metabolic or genetic predisposition to dyskeratoses.

(b) A genetic tendency towards a dyskeratosis and oligophrenia (particularly mongolism) may be enhanced by vitamin A or other nutritional defect.

(c) An inherent (genetic) disorder in the foetus may prevent normal utilisation of vitamin A, leading to secondary changes expressed as oligophrenia and dyskeratosis.

(d) Both the oligophrenia and dyskeratosis may be due to disorders of the primitive ectoderm produced by one or more unfavourable genes. In this case the dyskeratosis and certain endocrine disturbances may represent an inability of ectodermal cells to handle the metabolism of vitamin A.

None of these theories can be conclusively proved or disproved at present and further evidence must be sought.

8. Some suggestions for further study of mental deficiency are given, arising out of the present paper and its conclusions. These include clinical and experimental studies, in particular endocrine and metabolic studies of mongoloids and their mothers. In addition, it is felt that large-scale trials of vitamin A and carotene administration in pregnancy are justified.

9. An optimistic attitude should be shown towards the investigation^{and} possible prevention or alleviation of some types of mental deficiency. It is not clear that genetic factors alone are responsible for the birth of all examples of primary amentia.

10. Even if the theories suggested should prove to be untenable their investigation will greatly increase our knowledge of mental

deficiency. In addition, the present paper emphasises the need for a better classification of the mental deficiencies, and the existence of a "cutaneous group" is supported.

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APPENDIX NO. 1

Brief notes on the patients in Gogarburn Hospital, found to have skin disorder of "dyskeratotic" type.

Case reports marked with an asterisk are examples of the Syndrome of Rud.

1. M. C. female aged 21.

Duration in hospital, 14 years. I. Q. 36 (Merrill-Palmer).

Skin shows keratosis follicularis.

Patient comes second in a sibship of six. The first child died aged 4 days and the doctor said that she would have been an imbecile. One paternal aunt is an imbecile. Nothing is known of skin disease in the family. Patient is undersized though well-nourished. There is no evidence of hypogonadism. She has received thyroid $\frac{1}{2}$ gr. b. d. for years, without effect on the skin condition.

2. K. H. female aged 19.

Duration in hospital 12 years. I. Q. 59 (Terman-Merrill).

Skin shows keratosis pilaris, plus an excessive thickening of the skin over the knees and elbows, which is unaccounted for by any extraneous pressure. No evidence of hypogonadism. Mother is said to be feeble-minded, and father spent 14 years in a mental hospital.

3. M. McK. female aged 28.

Duration in hospital 20 years. I. Q. 28 (Terman-Merrill).

Patient has epilepsy. Skin is described as "dry and harsh" at the time of her admission, but her nutrition was poor at that time. At the time of the present examination she was found to have keratosis

follicularis, also a marked thickening of the skin over the knees and elbows which was unaccounted for.

4. R. M. female aged 32.

Duration in hospital 20 years. I. Q. 31.

She has a generalised xeroderma, also an angioma on the left cheek. There is no epilepsy, and no evidence of hypogonadism. Patient is from a sibship of 6. One sister may be also mentally defective.

5. M. P. female aged 29.

Duration in hospital 14 years. Imbecile.

Skin shows keratosis follicularis, also marked xeroderma. No epilepsy nor evidence of hypogonadism. No family history known.

6. C. T. female aged 27.

Duration in hospital 7 years. Feeble-minded.

Skin shows a mild example of keratosis follicularis. She suffers from frequent major epileptic seizures. Nothing is known of her family other than that she has a normal twin brother.

7. A. D. female aged 31.

Duration in hospital 1 year. Imbecile.

This patient has mongolism, and the skin shows mild keratosis follicularis and dry scaly elbows and knees. One sister is known to be normal.

* 8. M. J. female aged 62

Duration in hospital 8 years. Imbecile.

Patient suffers occasional epileptic seizures. On admission to the

hospital, she was noted to have "very dry skin, patchy and scaling". At the time of examination had a mild ichthyosis. Has talipes equinovarus. No evidence of hypogonadism. No family history available.

9. S. McK. female aged 23.

Duration in hospital 1 year. Imbecile.

This patient has mongolism, and the skin shows a generalised xeroderma. She is the last living child of a sibship of 4. The mother was aged 40 at the time of the patient's birth.

10. J. McL. male aged 64.

Duration in hospital 18 years. Imbecile.

Patient has a congenital malformation of all the nails which are unusually small and heaped up. He suffers from epilepsy. No family known, and no history available.

11. G. D. male aged 39.

Duration in hospital 20 years. Imbecile.

This patient has mongolism and on admission was noted to have "rough skin". At present he is seen to have generalised xeroderma which varies in severity in different places. An elder sister is said to be normal.

12. D. McK. male aged 58.

Duration in hospital 24 years. Feeble-minded.

Skin shows ichthyosis, keratosis follicularis and anhidrosis in combination. There is pes cavus present. No family history available.

13. D. C. male aged 13.

Duration in hospital 7 years. Imbecile.

Skin shows generalised xeroderma. Before his birth his mother had a stillbirth and an abortion. No other relevant history available.

14. G. B. male aged 23.

Duration in hospital 6 years. Idiot.

Skin shows keratosis follicularis. Patient was born without eyeballs and has bilateral talipes equinovarus.

15. W. S. male aged 50.

Duration in hospital 16 years. Imbecile.

Skin shows keratosis follicularis. One sister is normal; one is mentally defective.

16. R. S. male aged 30.

Duration in hospital 24 years. Low grade imbecile.

Skin shows ichthyosis most marked on the legs, also keratosis follicularis on other parts of the body.

17. J. B. male aged 51.

Duration in hospital 17 years. Imbecile.

Skin shows a dry scaly erythema which is aggravated in summer time, apparently due to sensitivity to sunlight.

18. A. D. male aged 15.

Duration in hospital 9 years. I. Q. 58 (Terman-Merrill).

Generalised xeroderma with patches of mild ichthyosis and keratosis follicularis.

19. W. H. male aged 29.

Duration in hospital 16 years. Imbecile.

Skin shows keratosis follicularis.

20. W. H. male aged 30.

Duration in hospital 3 years. Feeble-minded.

Keratosis pilaris with localised ichthyosis of knees, elbows, and thighs. One brother attends a special school, and one is known to be definitely mentally defective.

21. W. M. male aged 25.

Duration in hospital 16 years. Imbecile.

Xeroderma over almost all of the body. Slight axillary sweating occurs.

22. E. J. male aged 28.

Duration in hospital 18 years. Imbecile.

This patient has mongolism. The clinical notes describe him as having suffered from a "dry eczematous rash on the trunk and neck". At present he suffers from ichthyosis which is mainly present on the feet, arms, and neck. Two younger siblings are healthy.

23. J. P. male aged 29.

Duration in hospital 14 years. Imbecile.

This patient has mongolism. The skin was noted to be dry and scaly on admission to hospital. At present he has an ichthyosis mainly localised to the thighs. Five younger siblings are normal.

24. M. W. female aged 39.

Duration in hospital 15 years. Imbecile.

Severe keratosis pilaris associated with generalised xeroderma.

Patient is known to have two normal siblings.

25. C. S. female aged 26.

Duration in hospital 10 years. Imbecile.

Skin shows generalised xeroderma and mild keratosis follicularis.

Mother is of low intelligence. A maternal aunt and a sister are mental defectives.

* 26. M. B. female aged 20.

Duration in hospital 8 years. I. Q. 68 (Terman-Merrill).

Skin of trunk is xerodermic; marked ichthyosis on legs and thighs; keratosis follicularis on thighs, arms and shoulders. Xeroderma and patchy ichthyosis of shoulders and arms. Patient is an aggressive epileptic, suffering an average of 3 seizures per week. Mother and maternal grandmother are also mental defectives, and patient's brother (case No. 51) is feeble-minded. No family history of any skin abnormalities. Patient's skin has appeared unchanged during her 8 years in hospital. She is of small stature but shows no evidence of hypogonadism.

27. L. K. female aged 39.

Duration in hospital 18 years. Low grade imbecile.

Ichthyosis is localised to the feet and arms. Menstruation irregular. Mother and five siblings are said to be normal. This case was classified as a primary mental defective in the hospital records, and is regarded as such for the purposes of the present survey. However, there is a vague history of blows to the head, and an illness considered

to be "possibly brain fever".

28. M. W. female aged 20.

Duration in hospital 14 years. Feeble-minded.

Skin shows generalised xerosis and keratosis follicularis. No history known.

29. M. M. female aged 30.

Duration in hospital 14 years. Feeble-minded.

The case notes record this patient as suffering from a prolonged "dry eczema", and at the time of examination there was a marked generalised xeroderma present. No evidence of hypogonadism. The mother is said to have suffered from "fits". There are 4 healthy siblings. One sibling died from convulsions aged 6 months. Another died from heat-stroke aged 7 years (which suggests the possibility of ichthyosis or anhidrosis).

* 30. M. T. female aged 51.

Duration in hospital 26 years. Feeble-minded.

Skin shows generalised xeroderma with areas of considerable scaling.

This patient is an epileptic, suffering from about one seizure monthly.

No evidence of hypogonadism. No family history.

31. E. Y. female aged 27.

Duration in hospital 14 years. I. Q. 56.

Suffers from keratosis follicularis. No family history.

32. M. L. female aged 38.

Duration in hospital 29 years. Feeble-minded.

Suffers from keratosis follicularis. Mother and 5 siblings are said to be healthy.

33. R. R. female aged 34.

Duration in hospital 20 years. Imbecile.

Very scaly ichthyotic thighs. No family history.

34. A. M. female aged 40.

Duration in hospital 24 years. Imbecile.

Ichthyosis of legs. Marked xeroderma of upper limbs.

No family history.

35. L. H. female aged 42.

Duration in hospital 16 years. Feeble-minded.

Generalised xeroderma. No family history.

36. D. R. male aged 31.

Duration in hospital 15 years. Feeble-minded.

Keratosis follicularis. No family history.

37. H. R. male aged 40.

Duration in hospital 22 years. Feeble-minded.

Generalised xeroderma. No family history.

38. D. McG. male aged 41.

Duration in hospital 24 years. Feeble-minded.

Severe xeroderma throughout body, except for the palms.

No family history available.

39. T. S. male aged 44.

Duration in hospital 18 years. Feeble-minded.

A mild case of keratosis follicularis. Patient suffers from epilepsy.

40. D. W. male aged 30.

Duration in hospital 14 years. Feeble-minded.

Keratosis follicularis. No family history available.

41. J. C. male aged 29.

Duration in hospital 18 years. I. Q. 28.

Xeroderma and keratosis follicularis. Patient is a microcephalic epileptic. Mother, an aunt and an uncle are said to be epileptic, and may be mentally defective. Four siblings are said to be healthy, and one is dumb and was paralysed from birth.

42. A. R. male aged 28.

Duration in hospital 20 years. Imbecile.

Skin shows ichthyosis and keratosis pilaris. Patient suffers from mongolism and has cataracts. Three brothers are said to be healthy; two brothers died in infancy - one had spina-bifida.

43. A. S. male aged 49.

Duration in hospital 18 years. Feeble-minded.

Keratosis follicularis. Two siblings were stillborn; three are described as healthy.

44. R. T. male aged 27.

Duration in hospital 3 years. Feeble-minded.

Keratosis follicularis on upper and lower limbs; ichthyosis of thighs. Two elder brothers are normal. Following the patient, two siblings were stillborn.

45. D. R. male aged 17.

Duration in hospital 4 years. Feeble-minded.

A mild example of keratosis follicularis.

All that is known of the family is that one sister is said to be normal.

46. J. T. male aged 20.

Duration in hospital 6 years. Feeble-minded.

Suffers from mild keratosis follicularis. The only child of parents about whom little is known.

47. J. S. male aged 18.

Duration in hospital 2 years. Feeble-minded.

Suffers from mild keratosis follicularis. Is said to have a normal sister.

48. G. D. male aged 28.

Duration in hospital 18 years. Feeble-minded.

Suffers from keratosis follicularis, and is of markedly small stature. Is said to have 4 normal siblings.

49. J. C. male aged 25.

Duration in hospital 16 years. Feeble-minded.

Suffers from mild keratosis follicularis. No family history available.

50. A. D. male aged 25.

Duration in hospital 17 years. Feeble-minded.

Generalised xeroderma and mild keratosis follicularis. No family history available.

51. R. B. male aged 17.

Duration in hospital 5 years. Feeble-minded.

Brother of case No. 26. Suffers from mild generalised xeroderma which is more pronounced on the limbs where considerable scaling occurs.

Axillary sweating occurs. Patient is of small stature; body hair is poorly developed, and the genitals are small.

52. W. C. male aged 47.

Duration in hospital 15 years. Imbecile.

Suffers from mild keratosis follicularis. Ears are deformed and markedly unequal in size. No family history available.

53. A. H. male aged 30.

Duration in hospital 20 years. Imbecile.

Severe keratosis follicularis of arms and legs with ichthyotic patches on the legs. Is said to have a healthy younger brother.

The history mentions a suspicion that he showed failure of development following childhood diphtheria.

54. J. M. male aged 38.

Duration in hospital 4 years. Feeble-minded.

Generalised xeroderma and mild keratosis follicularis. No family history available.

55. A. D. male aged 44.

Duration in hospital 20 years.

Suffers from mild ichthyosis and keratosis follicularis.

Is said to have a healthy elder sister.

56. B. B. male aged 59.

Duration in hospital 16 years. Imbecile.

Generalised xeroderma. No family history available.

57. H. McL. male aged 39.

Duration in hospital 12 years. Feeble-minded.

A mild case of keratosis follicularis. No family history available.

58. J. D. female aged 28.

Duration in hospital 18 years. Idiot.

Suffers from xeroderma and epilepsy. Has an underdeveloped uterus.

Is a case of congenital syphilis.

59. D. W. female aged 62.

Duration in hospital 18 years.

Skin was recorded as being "thin and dry" on admission. At present it shows keratosis pilaris and severe thickening of the skin of the knees and elbows, amounting to localised ichthyosis. Patient is epileptic and is considered to be a case of secondary mental deficiency with cretinism.

Only three of the above cases have been considered at any time to be examples of mental deficiency of the secondary type, namely, cases

numbered 53, 58, and 59.

The above cases are the only examples of the dyskeratotic type of skin disorder found among the Gogarburn patients. In addition, however, there were two females aged 19 and 39, both with adenoma sebaceum, associated with epiloia in each instance.

APPENDIX NO. 2

Brief notes on the patients (in the sample of 61 per cent of the population of the Butner Mental Defective Colony) who were found to have skin disorder of "dyskeratotic" type.

All patients had been hospitalised for at least several years.

Although intelligence quotients were stated for all patients, the test given was not always described. In some instances the I. Q. figure seemed to be markedly lower than the clinical condition suggested. I have therefore preferred to describe patients as idiots, imbeciles or morons (feeble-minded) depending on the clinical picture and the I. Q. report considered together.

Case No. 26 appears to be an example of the Syndrome of Rud.

1. L. M., male aged 49. Imbecile.

Marked generalised xeroderma.

Right-sided talipes equinovarus.

2. W. B., male aged 36. Mongol idiot.

Marked generalised xeroderma and severe hypohidrosis.

3. J. H., male aged 34. Idiot.

Marked generalised xeroderma with patches of severe ichthyosis on legs, thighs and arms.

4. D. P., male aged 63. Cretin imbecile.

Generalised xeroderma in spite of thyroid medication.

5. H. C., male aged 60. Imbecile.

Generalised xeroderma.

6. R. H., male aged 34. Mongol idiot.

Probably the most pronounced example of generalised keratosis follicularis (Darier's disease) seen in the whole series. Onychogryphosis of toe nails.

7. R. H., male aged 32. Mongol idiot.

Keratosis follicularis over all limbs and abdomen.

8. H. McC., male aged 31. Mongol idiot.

Generalised xeroderma with marked keratosis follicularis on lower limbs.

9. C. R., male aged 57. Imbecile.

Generalised xeroderma with marked keratosis follicularis on lower limbs.

10. L. T., male aged 45. Imbecile.

Generalised xeroderma.

11. B. H., male aged 52.

Severe generalised ichthyosis, said to have been "always present."

Has had treatment with vitamins without relief.

12. B. J., male aged 24. Mongol imbecile.

Generalised xeroderma with keratosis follicularis on lower limbs and marked hypohidrosis. Supernumerary distal phalanx on right thumb.

13. B. M., male aged 23. Mongol imbecile.

Generalised xeroderma. Pachyderma marked over elbows and knees without apparent cause.

14. W. R., male aged 28. Mongol idiot.

Keratosis follicularis on all limbs, abdomen and gluteal regions.

15. D. W., male aged 22. Epileptic imbecile.

Generalised xeroderma with marked patches of keratosis follicularis especially over the chest.

16. B. B., female aged 28. Mongol idiot.

Generalised xeroderma.

17. D. B., female aged 28. Imbecile.

Generalised xeroderma. Dystrophy of 2 finger nails.

18. A. P., female aged 75. Imbecile.

Generalised xeroderma with severe ichthyosis of arms and legs.

19. J. W., female aged 23. Mongol imbecile.

Generalised xeroderma.

20. M. F., female aged 51. Imbecile.

Xeroderma on all limbs and very markedly present on trunk.

21. L. F., female aged 52. Low grade moron.

Marked generalised xeroderma.

22. A. G., female aged 25. Imbecile.

Mild generalised xeroderma, pachyderma of elbows. Normal axillary sweating.

23. H. J., female aged 53. Mongol imbecile.

Generalised xeroderma, very marked on legs, thighs, buttocks and trunk.

Hypotrichosis.

24. M. S., female aged 30. Imbecile.

A mild example of congenital spastic diplegia.

Xeroderma of legs, thighs, buttocks. Pachyderma of elbows.

25. C. W., female aged 51. Imbecile.

Generalised xeroderma, ichthyosis of legs and thighs.

26. M. M., female aged 39. Epileptic imbecile.

Generalised xeroderma with severe ichthyosis on arms, shoulders, back, buttocks, thighs and legs. No real improvement although treated with a cod liver oil ointment.

This patient appears to show another example of the Syndrome of Rud.

27. L. P., female aged 48. Idiot.

Generalised xeroderma with ichthyosis over legs and thighs.

28. M. D., female aged 44. Imbecile.

Generalised xeroderma, very marked on legs, thighs and buttocks.

29. L. G., female aged 59. Imbecile.

Generalised mild xeroderma.

30. C. G., female aged 35. Mongol imbecile.

Generalised mild ichthyosis.

31. S. P., female aged 50. Idiot.

Generalised xeroderma with ichthyosis of legs and arms.

32. L. W., female aged 51. Mongol idiot.

Generalised xeroderma affecting even skin of face which is slightly thickened and very wrinkled.

Only in two of the above cases (nos. 4 and 24) is there any evidence that we are dealing with examples of the secondary type of mental deficiency. Indeed these were the only two sufferers from dyskeratoses who had been definitely recorded as secondary aments according to the Training School files.

APPENDIX NO. 2 a

Brief notes on persons (in a small sample of the population of North Carolina) found to have skin disorder of "dyskeratotic" type. (Control group 2 a).

1. A. G., female aged 74.

General health stated to be fairly good.

Mild generalised xeroderma.

2. B. D., female aged 45.

Suffering from a depressive psychosis. History of several months' anorexia.

Nutrition poor.

Generalised xeroderma.

3. G. D., female aged 40. Psychoneurosis.

Has thyroidectomy scar. Appearance of hair and eyebrows suggested hypothyroidism.

Generalised xeroderma.

(Unfortunately, I was unable to follow this case or to obtain laboratory data).

APPENDIX NO. 2 b

Brief notes on the patients in the State Hospital at Butner, North Carolina (chronic psychiatric patients) who were found to have skin disorder of "dyskeratotic" type. (Control group 2 b).

Cases indicated by an asterisk are of patients who are basically mentally defective and who have been omitted from the present statistical study.

1. H. B., male aged 49. General paresis.

In hospital 14 years.

Generalised xeroderma (this was noted on routine physical examinations 2 and 3 years previously).

* 2. W. W., male aged 31. Schizophrenic psychosis with mental deficiency.

In this hospital 3 years.

Attended a special school for the educationally subnormal.

Skin shows keratosis follicularis of arms, lower abdomen, buttocks, thighs and legs.

3. M. McI., male aged 32. Paranoid schizophrenia.

In hospital 11 years.

Xeroderma on arms and mild keratosis follicularis on lower legs.

4. B. M., male aged 57. Schizophrenia.

In hospital 5 years.

Has had thyroidectomy at unknown date. In the last year has suffered from a chronic amoebic dysentery and is relatively malnourished.

Skin shows a mild degree of xerosis.

5. J. G., male aged 68. Schizophrenia.

In hospital 29 years.

Generalised xeroderma (this was noted on routine examination 3 years previously).

* 6. L. D., male aged 62. Schizophrenic psychosis with mental deficiency.

In hospital 10 years.

Localised keratosis follicularis on legs, slight xeroderma of arms.

7. G. S., male aged 45. Psychopath with psychotic episodes.

In hospital 11 years.

Generalised xeroderma.

8. E. G., male aged 68. Manic-depressive psychosis.

In hospital 1 year on this occasion.

Slight xeroderma of arms; follicular keratosis on thighs.

9. A. K., male aged 68. Melancholia and arteriosclerosis.

In hospital 2 years.

Generalised xeroderma; onychogryphosis of toe nails.

Skin recorded as "atrophic" in 1952, "dry and scaly" in 1953.

Has not improved with E. C. T. and is still a feeding problem, suffering from anorexia and refusal of food.

10. I. B., female aged 66. Paranoid schizophrenia.

In hospital 18 years.

Leucotomised several years ago.

Mild xeroderma on body, fairly severe xerosis of skin of limbs.

- * 11. N. E. female aged 51. Chronic neurosis.

"Repeated several grades at school several times, but never succeeded in her school work." Showed behaviour disorders when younger. Now is very hypochondriacal and throws temper tantrums. No psychotic features. General knowledge far below average. Mild generalised xeroderma.

- * 12. E. W., female aged 65. Catatonic schizophrenia and mental deficiency.

In hospital 24 years.

Reached fourth grade at school and was regarded as being "simple and childish" until over the age of 20, at which time psychotic features appeared.

Generalised xeroderma, with slight scaling over legs.

- * 13. M. B., female aged 65. Arteriosclerotic dementia; mental deficiency.

In hospital 7 years.

Had a very poor school record, and I. Q. was recorded as 66 many years before present illness.

Skin shows mild generalised xerosis, worse on the limbs (was noted to be "inelastic" in 1949).

14. L. H., female aged 69. Arteriosclerotic dementia.

In hospital 3 years.

Generalised xeroderma.

15. S. S., female aged 64. Schizophrenia.

In hospital 20 years.

Considerable xeroderma of legs and arms. Thighs are also involved, but skin of trunk is normal.

16. M. V., female aged 72. Schizophrenia.

In hospital 30 years.

Generalised xeroderma.

17. L. C., female aged 60. Paranoid schizophrenia.

In hospital 20 years.

Mild generalised xeroderma.